UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF INDIANA
INDIANAPOLIS DIVISION

ELI LILLY AND COMPANY,	)	
	)	
Plaintiff,	)	
	)	
vs.	)	1:06-cv-1017-SEB-JMS
	)	
TEVA PHARMACEUTICALS USA, INC.,	)	
	)	
Defendant.	)	

FINDINGS OF FACT AND CONCLUSIONS OF LAW FOLLOWING BENCH TRIAL

This matter is before the Court for decision on the issues of validity, enforceability, and infringement of various patents held by Plaintiff, Eli Lilly and Company ("Lilly"). Lilly holds an approved New Drug Application ("NDA") No. 20-815 directed toward the use of raloxifene hydrochloride 60 mg tablets for the prevention or treatment of osteoporosis in post-menopausal women. Lilly markets the product disclosed in NDA No. 20-815 under the tradename EVISTA®. In connection with this NDA, Lilly listed twelve patents in the Orange Book, including: U.S. Patent Nos. 5,393,763 ("the '763 patent"); RE39,049 ("the '049 patent"); 5,457,117 ("the '117 patent"); RE38,968 ("the '968 patent"); 5,478,847 ("the '847 patent"); RE39,050 ("the '050 patent"); 6,458,811 ("the '811 patent); 6,797,719 ("the '719 patent"); 6,894,064 ("the '064 patent"); 6,906,086 ("the '086 patent"); 5,811,120 ("the '120 patent"); and 5,972,383 ("the '383 patent") (collectively, "Lilly's raloxifene patents").

Defendant, Teva Pharmaceuticals USA, Inc. ("Teva"), subsequently filed an Abbreviated New Drug Application ("ANDA") No. 78-193 with the FDA for raloxifene hydrochloride 60 mg tablets for the prevention of osteoporosis in postmenopausal women. Teva sought FDA approval to market its generic raloxifene hydrochloride product before expiration of the patents Lilly listed in the Orange Book. Pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), Teva's ANDA included a "paragraph IV certification" to Lilly's raloxifene patents, in which Teva certified that each of Lilly's raloxifene patents is invalid, unenforceable, or would not be infringed by Teva's manufacture, use, or sale of its generic raloxifene product.

After receiving notice of the ANDA filing and paragraph IV certification, Lilly brought this suit against Teva for infringement of the '086 patent, the '968 patent, and the '049 patent (collectively, "the bone loss patents"); the '050 patent ("the low dose patent"); and the '811 patent, the '719 patent, and the '064 patent (collectively, "the particle size patents"). The bone loss and low dose patents cover the oral administration of raloxifene hydrochloride for prevention or treatment of postmenopausal osteoporosis. The particle size patents cover pharmaceutical compositions containing raloxifene particles having a certain size distribution. Teva concedes infringement of the bone loss patents and the low dose patent if they are found valid and enforceable, but challenges their validity and enforceability on the following grounds: obviousness, lack of enablement, and inequitable conduct. With regard to the particle size patents, Teva contends that its generic raloxifene product does not infringe, and that even if its product

did infringe, the particle size patents are invalid on the basis of obviousness and lack of enablement.

The hearing on Lilly's motions for a temporary restraining order and preliminary injunction was consolidated with the trial, which was conducted to the Court over eleven (11) days, between March 9, 2009, and March 24, 2009. On the opening day of trial, Teva notified the Court that it had received notice of final approval from the FDA of its generic raloxifene product. On that same day, the Court entered a TRO prohibiting Teva from launching its generic raloxifene product in the United States for ten days, subject to extension based on the duration of Lilly's proofs in support of its motion for preliminary injunctive relief. On the second day of trial, Teva informed the Court that it would voluntarily withhold launch of its generic raloxifene product until April 23, 2009, in order to allow the Court to have a sufficient opportunity to rule on the preliminary injunction issues. On April 22, 2009, the Court granted Lilly's renewed motion for injunctive relief, preliminarily enjoining Teva from launching its generic raloxifene product in the United States, effective beginning on April 23, 2009, until the issuance of the Court's final ruling on the merits.

On the last day of trial, a post-trial briefing schedule was set for submission of the parties' final findings and conclusions, post-trial briefs, and responses. The final submission was due on or before June 22, 2009 [Docket No. 595]. Having now considered the evidence adduced at trial and the parties' post-trial submissions, we hold, for the reasons set forth in detail below, that: (1) the bone loss patents are valid and

enforceable and Teva's proposed commercial raloxifene product infringes claims 1-3 of the '086 patent; claims 1, 3, and 4 of the '968 patent; claims 1, 2, 5-9, 11, 12, 19, 20, 28, 31, 33, and 34 of the '049 patent; (2) the low dose patent is valid and enforceable and Teva's proposed commercial raloxifene product infringes claims 1, 2, 5, 7, and 12-15 of the '050 patent; and (3) claims 1, 3, 6, 7, and 10 of the '811 patent and claims 1-3 of the '064 patent are invalid for lack of written description.

Findings of Fact

I. The Parties

Plaintiff, Lilly, is an Indiana corporation that has its principal place of business in Indianapolis, Indiana. It is engaged in the business of research, development, manufacture, and sale of pharmaceutical products throughout the world. Defendant, Teva, is a Delaware corporation engaged in the business of making and selling both innovative and generic drugs which it distributes in Indiana and throughout the United States.

II. The Patents in Suit

The '086 patent (PTX 11)[1] and the '968 patent (PTX 16), a reissue of U.S. Patent

[1] When used in this order, "PTX" refers to Plaintiff's trial exhibits, "DTX" refers to Defendant's trial exhibits, "LDX" refers to Plaintiff's demonstrative exhibits, and "TDX" refers to Defendant's demonstrative exhibits.

No. 5,457,117 (PTX 13), were issued to Larry Black. They were thereafter assigned to and are now owned by Lilly. PTX 348A; PTX 6A. The '049 patent (PTX 15), a reissue of U.S. Patent No. 5,393,763 (PTX 12), was issued to Larry Black and George Cullinan and was assigned to, and is now owned by, Lilly. PTX 5A. Collectively referred to as "the bone loss patents," these patents share a common specification and have an effective U.S. application filing date of July 28, 1992. Lilly asserted claims 1-3 of the '086 patent, claims 1, 3, and 4 of the '968 patent, and claims 1-2, 5-9, 11-12, 19-20, 28, 31, and 33-34 of the '049 patent. The parties agreed by stipulation to present evidence at trial regarding the bone loss patents on representative claims 1, 2, and 3 of the '086 patent.[2] Claim 1 of the '086 patent is representative and provides:

> 1. A method of inhibiting post-menopausal bone loss in a post-menopausal woman in need of treatment to prevent or treat post-menopausal osteoporosis comprising administering a single daily oral dose to said woman of an effective amount of . . . [raloxifene] hydrochloride.

PTX 11 at col. 20:2-8.

The '050 "low dose" patent (PTX 17), a reissue of U.S. Patent No. 5,478,847 (PTX 14), was issued to Michael Draper and Larry Black. It was assigned to, and is now owned by, Lilly. PTX 347A; PTX 352A at ¶ 9; PTX 2214. It has an effective U.S. filing date of March 2, 1994. Lilly asserted claims 1-2, 5, 7, and 12-15 of the low dose patent. The parties agreed by stipulation to present evidence at trial on representative claims 14

[2] Unless noted otherwise in this opinion, citations to the bone loss patents will be made to the '086 patent. For purposes of this litigation, Lilly has asserted claims 1, 2, and 3 of the '086 patent as representative claims.

and 15 of the '050 patent. Claim 14 of the low dose patent is representative and reads:

> 14. A method of preventing post-menopausal osteoporosis in a post-menopausal woman in need of treatment to prevent post-menopausal osteoporosis comprising administering to said woman a hydrochloride salt of . . . [raloxifene] in an amount of 60 mg/day.

PTX 17, col. 14:65-15:17.

The '811 (PTX 18), '719 (PTX 19), and '064 (PTX 20) patents (collectively "the particle size patents")[3] were issued to Gordon Arbuthnot, Brian Dalder, Kerry Hartauer, Wayne Luke, and Robert Stratford and were assigned to, and are now owned by, Lilly. Hartauer 1237:1-1238:24; PTX 350A. These patents share a common specification and have an effective U.S. application filing date of March 26, 1996. Lilly asserted claims 1-3, 6-7, and 10-12 of the '811 patent. By stipulation, the parties presented evidence at trial on representative claims 1, 3, 6-7, and 10 of the '811 patent. Claims 1 and 6 of the '811 patent are illustrative and read:

> 1. A compound of formula I [raloxifene] and pharmaceutically acceptable salts and solvates thereof, characterized in that the compound is in particulate form, said particles having a mean particle size of less than about 25 microns, at least about 90% of said particles have a size of less than about 50 microns.
>
> 6. A pharmaceutical composition comprising or formulated using a compound according to claim 1, or a pharmaceutically acceptable salt or solvate thereof, in combination with one or more pharmaceutically acceptable carriers, diluents or excipients.

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[3] The parties stipulated that, for purposes of this litigation, claims 1, 3, 6, 7, and 10 of the '811 patent and claims 1, 2, and 3 of the '064 patent represent all of the "asserted claims" for the particle size patents in this litigation. Lilly agreed that if these claims are invalid (which, for the reasons detailed below, the Court has determined to be the case), it will not assert against Teva any other claims of the '811, '064, and '719 patents.

PTX 18, col. 39:24-41; col. 40:37-41.

Lilly asserted claims 1-4 and 17-19 of the '719 patent and claims 1-3, 6, 8-9, and 11-12 of the '064 patent. By stipulation, the parties presented evidence at trial on representative claims 1-3 of the '064 patent. The claims of the '719 and '064 patents require a water-soluble diluent and surfactant. PTX 20, cols. 39-40. Claim 1 of the '064 patent is illustrative and provides:

> 1. A pharmaceutical composition comprising:
>
> a) 60 mg of [raloxifene hydrochloride] . . . in particulate form, said particles having a mean particle size of less than about 25 microns, at least 90% of said particles have a size of less than about 50 microns;
>
> b) a surfactant; and
>
> c) a water-soluble diluent.

PTX 20, col. 39:23-32.

All of these patented inventions are embodied in Lilly's EVISTA®, raloxifene hydrochloride for prevention and treatment of postmenopausal osteoporosis, introduced in the United States in 1998. PTX 1299. In September 2007, EVISTA® was also approved for reduction in the risk of invasive breast cancer in postmenopausal women with osteoporosis and in postmenopausal women at high risk of invasive breast cancer. Id.

III. The Markman Hearing

On June 11, 2008, following a Markman hearing, the Court issued its claim construction order construing definitions for disputed claim terms used in the particle size

patents. Pursuant to that order, the disputed claims are construed as follows:

Disputed Term	**Court's Construction**
surfactant	A compound that reduces the surface tension of liquids, or reduces interfacial tension between two liquids or a liquid and a solid.
water-soluble diluent	A pharmaceutically inert substance, capable of being dissolved in water, that increases the bulk of a tablet.
size	The equivalent spherical volume diameter of a particle as determined by laser light diffraction scattering.
mean particle size	Mean equivalent spherical volume diameter by laser light diffraction scattering.
less than about 25 microns	A measured value of less than **30.1** microns.
less than about 50 microns	A measured value of less than **67.4** microns.
between 5 and about 20 microns	A measured value between 5 microns and **24.1** microns.
between about 5 and about 25 microns	A measured value between **4.0** microns and **30.1** microns.
between about 5 and about 20 microns	A measured value between **4.0** microns and **24.1** microns.

In addition, the parties stipulated that: "At least about 90%" means "at least 85.5%."

Docket No. 158.

IV. The Bone Loss Patents[4]

[4] We discussed the facts related to the bone loss patents in our prior entry addressing Lilly's request for injunctive relief [Docket No. 636] and they have been altered here only to the extent required to reflect any changes necessitated by the Court's review of the parties' post-trial filings.

The bone loss patents relate to the administration of a class of drugs known as benzothiophenes, such as raloxifene and raloxifene hydrochloride, for the prevention of bone loss. PTX 11, col. 1:15-17. According to the bone loss patents, osteoporosis is one ailment that may occur as a result of bone loss. Osteoporosis is described as "a major debilitating disease whose prominent feature is the loss of bone mass (decreased density and enlargement of bone spaces) without a reduction in bone volume, producing porosity and fragility." PTX 11, col. 1:34-38. The bone loss patents characterize the benefits of the invention as follows: "the real benefit of the current discovery is that the benzothiophenes of formula I inhibit the loss of bone but do not elicit significant estrogenic responses in the primary sex target tissues." PTX 11, col. 3:15-18.

Definition of a Person Having Ordinary Skill in the Art for the Bone Loss Patents

A person having ordinary skill in the art to whom the bone loss patents are directed would be a person who has at least a Bachelor's degree in a scientific discipline who has experience performing, or has knowledge about, animal studies and their usefulness in osteoporosis research. Kinney 967:24-968:15. Because the specification of the '086 patent specifically defines and discusses the bioavailability problem associated with raloxifene and researchers in both the bone and cancer fields were publishing on the metabolism issues related to raloxifene and other compounds with free hydroxyl groups around the time of the invention, a person of ordinary skill in the art at the time would also necessarily have a general understanding of (*i.e.*, the person would be at least

conversant in) pharmacokinetics and ADME (absorption, distribution, metabolism, and excretion) characteristics and have a basic background knowledge of how those characteristics relate to the success of a drug. Lindstrom 447:11-16.

Postmenopausal Osteoporosis and Early Treatment of the Disease

The scientific evidence adduced at trial established that human bone is comprised of two types of bone tissue – trabecular bone, which consists of a lattice work of interconnecting rods and plates, and cortical bone, which is a more solid structure. Russell 74:14-25. Approximately twenty percent (by weight or calcium content) of the adult skeleton is comprised of trabecular bone; cortical bone makes up the other eighty percent. Russell 79:23-80:1. These two types of bone present differing biologies: trabecular bone is more metabolically active and is also particularly responsive to the hormone, estrogen. Russell 80:6-9.

Over time, human bones go through a number of changes, primarily due to growth and remodeling. Bone growth occurs lengthwise. During this process, cartilage is present at the region of the growth plate, becomes calcified, and is replaced by trabecular bone. By adulthood, almost all bones in humans have stopped growing because the growth plates have closed and new bone is no longer produced.[5] Russell 82:3-11. Bone

[5] In other species, such as rats, the growth plates remain open into adulthood, so the bones continue to grow to some extent even after the animal has reached adulthood. Russell 82:12-15.

remodeling is the process by which the trabecular portion of the bone is removed and then replaced, which changes both the shape and substance of the bone. Russell 82:21-23. Approximately ten percent of the trabecular bone is replaced every year so that, over a ten-year period, the trabecular portion of the bone is entirely replaced. Russell 80:21-24. The first stage of remodeling is bone absorption, whereby cells called "osteoclasts" essentially dig out part of the bone and remove it. The second stage of the remodeling process is bone formation, during which cells called "osteoblasts" replace the bone that was lost via absorption by laying down a protein substance like "collagen." Russell 83:11-84:6. In healthy adults, the skeletal mass remains constant throughout the remodeling process because the amount of bone that is lost is replaced in similar amounts. Russell 84:18-22.

However, when osteoporosis occurs, the replacement of bone during the remodeling process is incomplete, meaning that, at the completion of each remodeling cycle, more bone is removed than is replaced, causing a thinner bone. Russell 85:25-86:6. Thus, the structure of the osteoporotic bone is not as strong as a normal, healthy bone, which makes it prone to fracture; that is the ultimate consequence of osteoporosis. Russell 86:9-12. Osteoporosis is largely a consequence of a lack of sufficient estrogen in the system. Russell 87:10-11. Before menopause, estrogen slows the process of resorption and remodeling, essentially acting as a "brake" on the process. Russell 88:5-8. Following menopause, when women's bodies lose significant levels of systemic estrogen, the remodeling process becomes much more vigorous. Russell 88:7-9. Osteoporosis is a

relatively common condition: approximately one in two women beyond the age of fifty suffers an osteoporotic fracture at some point during the remainder of their lives. Russell 86:15-18.

Because osteoporosis results mainly from a lack of estrogen in the system following menopause, the principal treatment, historically, for postmenopausal osteoporosis has been estrogen replacement therapy ("ERT"). ERT successfully prevents bone loss as well as fractures. Russell 93:15-22. However, there are significant problems associated with ERT, including increased risk of both breast and uterine cancer. Russell 93:22-94:2. Therefore, researchers perceived a need and an opportunity to develop a drug to treat and prevent postmenopausal osteoporosis, which would act like estrogen in preventing bone loss but would not cause such damaging side effects in other tissues.

Early Development of Antiestrogens for Use in the Treatment of Breast Cancer

The class of compounds known as antiestrogens, which includes raloxifene, were originally developed to be used in the treatment of estrogen-dependent breast cancer. A large number of breast cancers are estrogen dependent, which means that estrogen stimulates their growth. Estrogen-dependent breast cancer cells contain so-called estrogen receptors. Endogenous estrogen, that is, estrogen found naturally within the body, binds to those receptors, stimulating the cancer cells and promoting growth of the cancer. Antiestrogens work to inhibit the growth of the cancer by binding to the estrogen receptors, thereby blocking the action of the estrogen. Russell 95:4-96:7; 99:9-100:6.

Some antiestrogens are very potent, allowing only a small amount to displace the natural estrogen. Others are weaker, requiring larger amounts to create the desired effect. Russell 97:13-15.

By the 1970's, two antiestrogen compounds, clomiphene and tamoxifen, were being investigated for their potential anti-cancer effects. Tamoxifen became one of the first clinically successful antiestrogens used in the treatment of breast cancer. Russell 100:10-11. However, side effects developed from various antiestrogens, including tamoxifen, that were similar to the side effects of estrogen, itself. Russell 102:10-12. Researchers discovered that, when certain antiestrogens were not competing with estrogen for the receptor (i.e., when there was little estrogen already in the system, such as in postmenopausal women), the antiestrogens, themselves, could interact with the estrogen receptors and display estrogenic properties of their own. Russell 102:10-103:2. For example, in the absence of estrogen, antiestrogens were found still to have a stimulatory estrogenic effect in the uterus, which was ultimately associated with an increased risk of endometrial cancer. Various antiestrogens mimic the effect of estrogen in varying degrees, and the degree to which a particular antiestrogen mimics estrogen is referred to as its intrinsic estrogenicity. Russell 102:13-15. Tamoxifen, for example, has significant intrinsic estrogenicity; thus, despite being an antiestrogen, at sufficiently high doses it can produce an effect roughly equivalent to forty percent of the effect of estrogen itself. Russell 103:5-14; 103:23-104:2.

Early Development of Raloxifene for Use in the Treatment of Breast Cancer

Because of concerns associated with these estrogen-like side effects, researchers at Lilly, including Larry Black, set out to find a purer antiestrogen that would have positive effects in breast tissue, but lesser effects in the uterus. Larry Black, Lilly's inventor, received a Bachelor of Science degree in biological sciences from Indiana Central College in 1966. He joined Lilly in 1966, where he remained employed until his retirement in December of 1993. Black 107:23-109:22. During the 1970's and 1980's, Mr. Black worked as a research scientist evaluating antiestrogen compounds, initially for use in the treatment of breast cancer. Black 110:13-111:1.

In the late 1970's, Mr. Black and another Lilly scientist, Dr. C. David Jones, began their research on the antiestrogenic properties of a family of molecules known as "benzothiophenes." One of the compounds within that family, known to the researchers only by its Lilly compound number "LY117018,"[6] displayed potential for development. Black 115:2-6. In November 1979, in the course of exploring the properties of molecules structurally related to LY117018, Dr. Jones first synthesized, and Mr. Black subsequently tested, the molecule now known as raloxifene; at that time, it was referred to only by its Lilly compound number "LY139481," which was an analog of LY117018.[7] Black

[6] Every compound synthesized by Lilly chemists is assigned an "LY" number for purposes of identification. If a certain molecule progresses through development to the point where it will be used in clinical studies, a name for the compound is then assigned. Black 116:6-21.

[7] The compound LY139481, which eventually became "raloxifene," was first called

(continued...)

131:20-132:18. The chemical structures of LY117018 and raloxifene are virtually identical.

Unlike tamoxifen, both LY117018 and raloxifene contain free hydroxyl groups, the significance of which is discussed below. The chemical structure of raloxifene differs from LY117018 only in that the former has a six-membered nitrogen-containing ring, whereas the latter has a five-membered nitrogen-containing ring. Mr. Black determined that this difference gave raloxifene (LY139481) an improved activity profile, meaning that it had a higher affinity for the estrogen receptor, a lower intrinsic estrogenicity, and a greater ability to antagonize estrogen. Black 115:19-116:5; 117:11-17.

In 1980, a project team[8] was formed at Lilly to bring raloxifene through clinical trials for treatment of breast cancer. In the course of development, Lilly scientists discovered that the hydrochloride salt of raloxifene, identified as "LY156758," was easily prepared and had somewhat better water solubility. Thus, the decision was made by Lilly scientists to work with raloxifene hydrochloride, which ultimately became the active ingredient in EVISTA®. In 1982, Mr. Black published his findings relating to raloxifene and its hydrochloride salt in an abstract of a presentation he delivered at the San Antonio

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[7](...continued)
"keoxifene." While the documentary evidence often uses the term "keoxifene," we have utilized the current name of the compound, "raloxifene," for sake of clarity and consistency throughout this opinion.

[8] At Lilly, "project team status" is acquired when the Project Team Approval Committee (PTAC) determines that sufficient information has been gathered to demonstrate a true potential for clinical activity for a particular compound. Black 118:19-119:5.

Breast Cancer Symposium, entitled "LY156758: A Unique Antiestrogen Displaying High Affinity for Estrogen Receptors, Negligible Estrogenic Activity and Near-Total Estrogen Antagonism *In Vivo*." PTX 1625. In that abstract, Mr. Black reported that raloxifene produced a very minimal increase in uterine weight (one measure of a compound's intrinsic estrogenicity) in rats, while tamoxifen caused marked uterine growth. Additionally, he reported that raloxifene did not show any stimulatory effect on the luminal epithelial cells (another measure of a compound's intrinsic estrogenicity). Id.; Black 134:22-136:1.

Bioavailability Issues Associated With Raloxifene[9]

The pharmacokinetics of a compound, which term refers to the compound's absorption into the systemic circulation, its distribution throughout the body followed by its metabolism or conversion into other forms, and excretion out of the body ("ADME characteristics"),[10] present important considerations when determining whether and how to develop a drug for human clinical use. This is because a significant number of drug candidates fail in clinical trials due to ADME problems. Lindstrom 328:3-11; 337:4-18.

[9] Although the bioavailability issues associated with raloxifene were not addressed during prosecution of the bone loss patents, the Federal Circuit has held that a patentee is not limited only to those arguments in support of patentability that were made before the PTO. TorPharm, Inc. v. Ranbaxy Pharm., Inc., 336 F.3d 1322, 1330 (Fed. Cir. 2003).

[10] "ADME" is an acronym for absorption, distribution, metabolism, and excretion. Lindstrom 327:23-328:1.

Thus, in order to optimize bioavailability in humans, Lilly researchers looked for compounds with low metabolism rates that would be well absorbed. Lindstrom 337:13-18. Due in large part to the two free hydroxyl groups in its chemical structure, however, raloxifene proved to be highly metabolized in the liver, that is, the parent compound was converted into a glucuronide conjugate that was rapidly excreted from the body. Lindstrom 341:15-342:7; 342:16-21; 343:13-344:6. In the vast majority of compounds, this process of glucuronidation serves to deactivate the drug. Hayton at 1186:2-5. It was known, in any event, prior to the issuance of the '086 patent, that at least one compound, morphine-6, was active in conjugated form (Hayton 1186:6-11) and that certain enzymes could in some cases reverse the effects of conjugation. Black 139:24-140:7.

In preparation for developing raloxifene for the treatment of breast cancer, data relating to raloxifene's bioavailability was discovered from pre-clinical animal tests performed by Dr. Terry Lindstrom, a member of Lilly's raloxifene project team. In January 1983, in an abstract entitled "Disposition and Metabolism of a New Antiestrogen, LY156758, in Rats, Dogs, and Monkeys," and also in 1984, in a comprehensive journal article entitled "Disposition and Metabolism of a New Benzothiophene Antiestrogen in Rats, Dogs, and Monkeys," Dr. Lindstrom published the results of various animal studies he had conducted using raloxifene in which he found that the bioavailability of the parent raloxifene was approximately 39% in rats, 17% in dogs, and 5% in monkeys. Dr. Lindstrom further noted that in monkeys "the compound occurred primarily as the glucuronide conjugate of parent [raloxifene] with very little circulating free drug." PTX

684 at EV 7002 956. However, Dr. Lindstrom's study did not test whether, despite the bioavailability problem, raloxifene had any effect on the animals. Lindstrom 435:11-15.

In the drug development process generally, before clinical trials in patients can begin, a compound must first be tested for safety through so-called "Phase I" tests. Thus, before raloxifene could be developed for human use, it had to undergo Phase I pharmacokinetic testing in humans. Lindstrom 472:8-472:18. In September and October 1982, in preparation for testing raloxifene for clinical purposes, Lilly completed a Phase I test of raloxifene using doses of up to 200 mg in male human volunteers. The results of these tests, as reported in Lilly's internal documents, revealed that, although a considerable amount of the conjugate glucuronide was present in the serum of the human volunteers, attempts to measure the parent raloxifene had been unsuccessful. PTX 594 at EV 141 341; PTX 816 at EV 7250 215. Lilly conducted a second test in male human volunteers in which a 200 mg dose of raloxifene was administered once daily for fourteen days, but levels of parent raloxifene still could not be measured. PTX 597 at EV 141 577.

In 1985, raloxifene was given for the first time to humans for clinical purposes in a study conducted by Dr. Aman Buzdar. That study involved giving raloxifene to female breast cancer patients whose cancer had not responded to tamoxifen. In a 1988 article entitled "Phase II Evaluation of Ly156758 in Metastatic Breast Cancer," Dr. Buzdar published the results of his study, reporting that, with the exception of one minor

response, there were no complete or partial responses to raloxifene.[11] From these results, Dr. Buzdar concluded that raloxifene "did not show any antitumor activity in this study and no further revaluation of this drug is recommended." PTX 437. Dr. Buzdar did note toxicity results suggesting possible drug effects, including the existence of hot flashes, fatigue, leg cramps, and mild nausea. Id. However, there was no placebo control group in Dr. Buzdar's study, so there was no way to ascertain the existence or frequency of these side effects in untreated women. Kinney 1088:6-24. Although Dr. Buzdar's reports do not attribute raloxifene's lack of efficacy to a bioavailability problem, some Lilly researchers, such as Dr. Lindstrom, believed that to be the cause. Lindstrom 366:9-367:4.

In August 1987, Alan Schreiber and George Farnbach from the University of Pennsylvania visited Lilly to discuss developing raloxifene for the treatment of autoimmune diseases. A group of Lilly scientists who had been associated with the raloxifene clinical trial was convened to discuss Dr. Schreiber's proposal. In an internal memorandum, the group explained its reasons for rejecting the proposal, including their belief that, in light of the rapid glucuronide conjugation, it was "highly unlikely that sufficient [raloxifene] would be available in the serum to have any clinical effect." PTX 796 at EV 7245 55. On October 5, 1987, Lilly's rejection of Dr. Schreiber's proposal was

[11] Trioxifene, an antiestrogen that, unlike raloxifene, does not contain the hydroxyl groups that make the compound subject to conjugation, had previously been administered by Dr. Buzdar to tamoxifen-resistent patients and had shown an objective response. PTX 437. Based on the knowledge that raloxifene had previously been shown to have a higher affinity for the estrogen receptor than either tamoxifen or trioxifene, Dr. Buzdar's Phase II study of raloxifene was initiated. Id.

communicated by letter to Dr. Farnbach, which stated: "Not insignificant in our consideration of [raloxifene] are the disappointing bioavailability results observed during our Phase I clinical trial." PTX 1203 at EV 7419 7.

Throughout this time period, a number of researchers outside Lilly also published on raloxifene's rapid metabolic conversion. For example, in 1983, in an article entitled "Antioestrogenic and Antitumour Activities of a Series of Non-Steroidal Antioestrogens," A.E. Wakeling and B. Valcaccia address the decreased potency of several compounds, including raloxifene, when administered orally versus when administered subcutaneously. Wakeling stated that:

> Metabolic differences may account for these discrepancies, since, in contrast to tamoxifen and trioxifene, both LY 117018 and LY 139481 [raloxifene] have free hydroxyl groups [citations omitted]. These compounds are likely to be susceptible to rapid conjugation and excretion, particularly when administered orally.

PTX 673 at EV 50 1039.

Dr. Craig Jordan also published on this issue. In 1983, in an article entitled "Differential Antiestrogen Action in the Immature Rat Uterus: A Comparison of Hydroxylated Antiestrogens with High Affinity for the Estrogen Receptor," Dr. Jordan and B. Gosden stated that:

> With regard to pharmacokinetics, LY117018 [the benzothiophene dihydroxyl analog of raloxifene] is a dihydroxylated antiestrogen and, as such, would be expected to be more rapidly conjugated and excreted than monohydroxytamoxifen. . . . This in fact seems to be the case as LY117018 is excreted from the immature rat five times more rapidly than monohydroxytamoxifen [citations omitted]. If monohydroxytamoxifen is considered to be a short-acting antistrogen compared with tamoxifen

> [citation omitted] then LY117018 should be classified as an ultra short-acting estrogen antagonist.

PTX 913 at 1257. In 1984, Dr. Jordan published a review article entitled "Biochemical Pharmacology of Antiestrogen Action" in which he discussed the hydroxylation of compounds such as raloxifene and stated that "[c]learly this will facilitate a rapid metabolism and excretion of those compounds." PTX 843 at EV 8521 12448.

The results discussed above from Lilly's Phase I testing, in which a significant amount of the conjugate glucuronide was present in the serum of the human volunteers, but no parent raloxifene was measured, were cited in a 1987 article entitled "Hormonal Modulation of Macrophage Clearance of IgG-Sensitized Cells," by M.C. Sanders, A.I. Levinson, and A.D. Schreiber. In that article, the authors report that, while raloxifene was well-tolerated in the studies, the compound "appears to have a short serum half-life, which may be a result of rapid biotransformation." PTX 844 at EV 8521 4134.

Black's Studies on the Glucuronide Conjugate of Raloxifene

In an effort to address the widely discussed concerns regarding the bioavailability of raloxifene, Mr. Black began to conduct studies to attempt to determine whether, despite its rapid conjugation, the compound could still have efficacy. In 1983, Mr. Black conducted a study on ovariectomized rats in which he lowered the oral dose of raloxifene administered until no parent was detected, yet a large amount of the glucuronide was present, which duplicated the conditions observed in the human subjects in Lilly's Phase I

testing. Despite there being no detectable parent in the serum, Mr. Black was able to measure an end-point response, to wit, an antiestrogenic effect in the uterus of the rat. Black 140:20-141:18; PTX 715. Mr. Black believed that these results showed that the mere fact that the parent was not detectable in the serum did not necessarily indicate that it could produce no effect. Black 141:18-20; see also PTX 715 at EV 7080 1133.

Later in 1983, Mr. Black obtained a sample of the raloxifene conjugate from the human subjects in the Phase I tests, which had been isolated from the urine collected from the subjects, which he administered intravenously into rats in an effort to reproduce the condition observed in the human subjects in which only the conjugate was present in the bloodstream. Black 142:25-143:19. Black's study included a control group and a second group that had been administered the parent raloxifene. The control group showed no effect, but the group administered the conjugate extract showed antiuterotropic activity similar to that caused by the parent compound. Black 143:10-144:8; PTX 817 at EV 7250 222. Thus, Mr. Black concluded that these results supported the conclusion that the lack of detectable parent compound does not necessarily preclude efficacy. Black 144:8-13. The results of this study were not published, but the study is discussed in the '086 patent. Black 145:1-4.

Mr. Black obtained a second sample of the human conjugate that had been extracted from the urine of the human subjects involved in the Phase I testing. Using that sample, Mr. Black conducted a study in which he evaluated the effect of the conjugate, the raloxifene parent, an estrogen control group, and a control extract on uterine tissue *in*

vitro, that is to say, in a test tube assay, to determine their respective abilities to bind directly to the estrogen receptor. Black 147:23-148:12. Mr. Black tested the groups at two temperatures--four degrees and twenty-five degrees--and incubated them for one hour, four hours, and twenty-four hours. Black 148:14-20. At four degrees, the estrogen and the parent raloxifene bound normally to the receptor, but neither the blank control nor the conjugate interacted with the estrogen receptor. At twenty-five degrees, the blank control still did not show activity. However, as the conjugate was incubated, it displayed increasing levels of response, and, by twenty-four hours of incubation, its competition for the estrogen receptor was similar to that in the estrogen control and parent raloxifene. Black 149-16-23; PTX 72 at EV 7243 1. From this series of experiments, Mr. Black concluded that, under physiological conditions, the conjugate observed in the human bloodstream could possibly be converted back to the parent compound. Black 151:7-13. The results of these experiments were not published but also were referenced in the '086 patent. Black 151:14-18.

The Prior Art to the Bone Loss Patents

A. The Beall Article

As various antiestrogens were being investigated and developed for clinical use in the treatment of breast cancer, researchers in the field began to hypothesize, based on data sharing, given that estrogen inhibits bone loss and antiestrogens, in some cases, act like estrogen, antiestrogens might also be effective in the treatment of osteoporosis. For

example, in 1984, Paula Beall, *et al.*, published an article entitled "Clomiphene Protects Against Osteoporosis in the Mature Ovariectomized Rat" ("the Beall Article"). PTX 1962. The Beall Article disclosed that clomiphene, a mixed estrogen agonist-antagonist, prevents reductions in calcium content, cortical thickness, and trabecular bone in the femurs of ovariectomized rats, and concluded that these results "suggest a possible new line of investigation of the use of antiestrogenic drugs as therapeutic agents for hormone-dependent osteoporosis in animals and humans." Id. at 123.

B. The Jordan Reference

Because clomiphene is a partial estrogen, it was unclear whether those estrogen-like properties were responsible for Dr. Beall's observed response on bone or whether other antiestrogens could also produce such an effect. PTX 218 at 31. In light of the concern that long-term tamoxifen treatment in breast cancer patients could lead to premature bone loss, following the publication of Dr. Beall's study, Dr. V. Craig Jordan conducted a similar study on intact and ovariectomized 9-month-old retired breeder rats to determine the effects of tamoxifen and raloxifene (then called "keoxifene") on bone density. In October 1987, the results of that study were published in an article authored by V. Craig Jordan, Erik Phelps, and J. Urban Lindgren entitled "Effects of anti-estrogens on bone in castrated and intact female rats" ("the Jordan Reference"). PTX 218.

The Jordan Reference reported that both tamoxifen and raloxifene inhibited bone loss in overiectomized rats and that raloxifene had a minimal estrogenic response in the

uterus. Dr. Jordan concluded that these results "may have important implications for the clinical [human] applications of antiestrogens." Id. at 34. He further stated that "[i]t is possible . . . that in the future, tamoxifen could be considered to be used as a substitute for estrogen [for the prevention of osteoporosis in postmenopausal women]." Id. Dr. Jordan called for clinical work to be conducted with tamoxifen to determine whether the results obtained in the rat studies would be applicable to humans:

> These contrasting pharmacological actions of antiestrogens suggest that patients receiving long-term adjuvant tamoxifen therapy for breast cancer should be evaluated to determine whether tamoxifen can retard the development of osteoporosis.

Id. at 31. The Jordan Reference did not discuss further development of raloxifene for the purpose of treating or preventing postmenopausal osteoporosis. At the time, only tamoxifen had been approved for clinical use in humans. Kinney 963:17-23.

C. The Feldmann Article

In 1989, in an article entitled "Antiestrogen and Antiandrogen Administration Reduce Bone Mass in the Rat" ("the Feldmann Article"), S. Feldmann *et al.* reported, contrary to the Jordan Reference, that raloxifene did not inhibit bone loss in ovariectomized rats and that tamoxifen produced an effect only at the highest dose administered. PTX 181 at 251. Dr. Feldmann noted that the lack of an effect observed with raloxifene "might be a dosage problem," but concluded that "an antiestrogen which does not show an estrogenic effect on sex organs, will not with respect to bones." Id. at

250-51. As discussed above, by the time the Feldmann Article was published, it was known in the field that raloxifene was a relatively pure antiestrogen that had a negligible estrogenic effect in the uterus.

D. The Turken and Love Articles

The 1987 article by Sheila Turken *et al.* entitled "Effects of Tamoxifen on Spinal Bone Density in Women With Breast Cancer" ("the Turken Article") disclosed the results of a study examining the effect of tamoxifen on the bone mineral density of the spine over one year of its administration to post-menopausal women with a history of breast cancer. PTX 1969. The Turken Article disclosed that tamoxifen preserved the spinal bone mineral density in the postmenopausal breast cancer patients, whereas healthy bone mineral control subjects experienced a significant loss of spinal bone mineral over the same period of time. Id. at 1088.

In March 1992, in an article entitled "Effects of Tamoxifen on Bone Mineral Density in Postmenopausal Women With Breast Cancer" ("the Love Article"), Richard Love *et al.* published results of a study on the effects of tamoxifen on spinal bone density in postmenopausal women with breast cancer. PTX 1917. Similar to the results disclosed in the Turken Article, Dr. Love disclosed that tamoxifen is associated with preservation of the bone mineral density of the lumbar spine in postmenopausal women. Id. at EV 8521 13098.

E. The Moon Article

In 1991, Lilly Moon *et al.* published an article entitled "Dose-Dependent Effects of Tamoxifen on Long Bones in Growing Rats: Influence of Ovarian Status" ("the Moon Article"). PTX 349. The Moon Article disclosed the results of a study testing the effects of tamoxifen on bone in intact and ovariectomized rats in which tamoxifen treatment prevented the decrease of trabecular bone volume in the ovariectomized rats, but resulted only in a small decrease in intact rats with the highest dose. Id. at 1568. Dr. Moon concludes that these results "are consistent with tamoxifen behaving as a partial estrogen agonist on rat bone." Id. The study published in the Moon Article did not test raloxifene, but with regard to tamoxifen, the authors conclude that their "findings are consistent with the results of Jordan *et al.* [citation to the Jordan Reference], who reported that tamoxifen reduced the decrease in femur ash weight/volume in adult OVX [ovariectomized] rats, but did not alter this measurement in intact rats." Id. at 1573. Distinguishing the conflicting results of tamoxifen's effect on bone in ovariectomized rats reported in the Feldmann Article, Dr. Moon criticized the measurement technique used in the study, the lack of a baseline control group, and the failure to include an estrogen-treated group in the study. Id. at 1573-74.

F. The '068 ("Jones") Patent

In 1981, Lilly filed an application that claimed the discovery of a class of compounds, including raloxifene. On November 29, 1983, the patent application issued

to Charles Jones as U.S. Patent No. 4,418,068 ("the Jones patent"). The Jones patent teaches that the claimed compounds have less inherent estrogenicity and cause fewer estrogenic side effects than earlier compounds, such as tamoxifen. PTX 2029 at col. 37:28-46. It also discloses that raloxifene can be administered in a pharmaceutical composition such as a tablet "formulated to contain a daily dose" (PTX 2029 at col. 39:7-11) and that it can be administered in dosages ranging from 0.05 mg/kg/day up to about 50 mg/kg/day. PTX 2029 at col. 38:55-58.

The Invention and the '086 Patent

In 1984, Mr. Black's raloxifene research shifted from the study of raloxifene's possible use in the treatment of breast cancer to a new therapeutic target, the menopausal syndrome, a component of which is postmenopausal osteoporosis. Black 154:23-155:7; 157:2-20. In February 1987, a proposal for Lilly's bone biology program targeted the investigation of the benzothiophene series of compounds in an effort to find an alternative to estrogen for the treatment of postmenopausal osteoporosis that would have advantages, such as reducing estrogenicity in the breast and uterus tissues, but that would also have an effect on bone and other menopausal problems. Black 160:2-18; see PTX 1806.

In March 1988, Mr. Black began his experiments to study the effects of raloxifene on bone in various ovariectomized rat models. Initially, he experienced difficulty in finding a validated animal model that would consistently demonstrate bone loss from

which it could then be shown to be prevented by estrogen.[12] Black at 173:17-22. In a series of experiments beginning in July 1988, Mr. Black used an older, retired breeder rat model, but found inconsistent results in his intact controls. In some of the experiments, he was unable to demonstrate bone loss upon ovariectomy with the retired rat model, but in other experiments, the retired breeder rats did show bone loss upon ovariectomy, which led him to conclude that the retired breeder rat was an unreliable model for bone loss.[13] Black 174:12-18.

Mr. Black next undertook similar experiments using an approximately 3-month-old virgin rat model,[14] which he determined showed bone loss with ovariectomy and prevention of the bone loss with estrogen.[15] Black 187:24-188:13. In March 1989, he

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[12] To ensure that a particular animal model is a proper model for studying osteoporosis, it is necessary to determine that the animal model is losing bone, similar to that which occurs in the osteoporotic woman, and that it has an estrogen sensitivity, like the osteoporotic woman, so that estrogen is able to inhibit that bone loss. Miller 512:12-513:4.

[13] Lilly's expert, Scott Cannon Miller explained that when the animals go through reproductive cycles, they lose a significant amount of trabecular bone due to lactation. After lactation, there is a recovery phase during which they recover their lost bone mass. Therefore, when using retired breeders, it is important to take their reproductive history into consideration, because, if a particular retired breeder rat has too recently been lactating, its trabecular bone may be so depleted that the rat is unable to show bone loss upon ovariectomy. Miller 513:23-514:15. Teva's expert, Dr. John Kinney, agreed that variability in the retired breeder rat model can occur, but that it does not automatically lead to unreliable outcomes if a baseline control study is performed and the experiment on the rats continues a sufficient period of time so that the transient effects due to lactation become less material. Kinney 1024:21-1025:14.

[14] The rats were received at 75 days old and were acclimated for one week before the experiments began. Black 187:6-11.

[15] As with the retired breeder model, there are also problems that can be associated with the younger rat model. For example, the rat grows more rapidly when it is younger, so a baseline (continued...)

studied the effects of raloxifene on the younger ovariectomized rat model, the results of which study revealed that the mean trabecular bone density observed for raloxifene was statistically significantly greater than the control. This finding led him to conclude that raloxifene prevented bone loss in that model. Black 191:1-23.

In November 1991, Lilly's PTAC approved a human clinical trial of raloxifene in postmenopausal women for the treatment of postmenopausal osteoporosis. Black 192:12-22. However, significant concerns regarding bioavailability issues were raised at the PTAC meeting relating to raloxifene. Many of the members were concerned about going forward with a compound that was associated with known ADME issues. According to Dr. Thomas Bumol, a member of PTAC at the time, the committee gave its approval for the clinical test despite these concerns, at least in part because Lilly already had an open IND on raloxifene, which would allow the clinical tests to be conducted within six months, rather than the usual twelve to twenty-four months. Bumol 491:5-492:7.

Before the results of the PTAC-approved clinical study had been collected, Lilly filed its patent application for the bone loss patents. Thus, there is no clinical human data included in the '086 patent. However, the PTAC-approved clinical study is described as Example 5 of the '086 patent, using doses of 200 mg per day and 600 mg per day. PTX 11 at col. 18:15-col. 19:20. Example 1 of the '086 patent explains Mr. Black's study on

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[15](...continued)
control study is necessary to determine whether the changes in bone are due to growth. Kinney 970:3-8.

ovariectomized rats and provides the mean results of assays using raloxifene in four different doses on thirty rats per dose. PTX 11 at col. 14:55-col. 16:10. The patent specification addresses the bioavailability issue and provides a rationale, derived from the results of the studies Mr. Black conducted in which he administered the glucuronide conjugate found in the bloodstream of the human subjects to rats, explaining the reason that the conjugation would not necessarily be detrimental to the efficacy of raloxifene in humans. PTX 11 at col. 3:28-60.

In May 1992, enrollment began for Lilly's Phase II, GGGB "proof of concept" study to test raloxifene's efficacy in humans described in Example 5 of the '086 patent. See PTX 339 at EV 133 2499. It was conducted by Dr. Michael Draper. The study ran from September 1992 to December 1992 and the results came back at the beginning of January 1993. Draper 683:14-684:1. Both the 200 mg and the 600 mg doses of raloxifene showed statistically significant changes in one or more of the bone markers tested, unequivocally demonstrating activity in humans. Draper 688:3-689:22.

The patent examiner twice rejected the original parent application to the '086 patent, based on the Jordan Reference. Following these rejections, Lilly scientist, Dr. Henry Bryant, submitted a declaration dated January 11, 1994, in which he asserted that, at the time of the invention, he would have had doubts about the conclusions set forth in the Jordan Reference because: (1) Dr. Jordan's statistical analysis was flawed; (2) the rats used in Dr. Jordan's research were an inappropriate model; (3) Dr. Jordan's measurement techniques were improper, and (4) Dr. Jordan was an expert in cancer, not in bone, and

his article was not published in a bone journal. PTX 217. On June 16, 1994, following a third rejection by the patent examiner, the Lilly patent attorney in charge of the prosecution of the bone loss patents at the time, James Sales, submitted a response to the PTO's final rejection, reiterating the criticisms raised in Dr. Bryant's declaration. PTX 2-TA at 430-31. The parent application to the '086 patent was subsequently allowed by the examiner.

Lilly's Criticisms of the Jordan Study

Lilly based its appeals of the PTO rulings on its view that the Jordan study was flawed in terms of making raloxifene obvious for the treatment of osteoporosis. Part of Lilly's criticism was based on the statistical methodology used by Dr. Jordan.

In the Jordan Reference, Lilly pointed out, the Student's t-test was used in the statistical analysis to compare five treatment groups. Lilly argued that the Student's t-test is an appropriate statistical method to evaluate differences between two groups and that a properly conducted Student's t-test would demonstrate that two groups are statistically different at a ninety-five percent confidence level. Miller 542:4-8; 543:11-15. However, as more and more groups are compared against the control, the likelihood increases that the Student's t-test will show a difference simply by chance, which is called a Type I error. Russell 650:10-23. Therefore, Student's t-test can appropriately be used to compare multiple groups when a publication concludes that a compound has no effect at all, because, when used on multiple groups, Student's t-test is more likely to show a

difference when there is not actually a difference than to inaccurately show no effect. Russell 649:2-18. Nevertheless, in exploratory drug research, it can be preferable to have a Type I error (false positive) over a Type II error (false negative) because the cost of a false positive is merely that further testing will show that the drug actually does not work, while the cost of a false negative is that a potentially valuable drug is eliminated from further study. Buncher Rep. ¶¶ 37-41.

As discussed above, depending on their reproductive history, retired breeders rats, such as those used in Dr. Jordan's study, can have varying levels of trabecular bone based on how recently they went through the lactation process. Also, as previously noted, when the animals go through reproductive cycles, they lose a significant amount of trabecular bone due to lactation. Following lactation, there is a recovery phase during which the rats recover their lost bone mass. Thus, if a retired breeder rat has too recently been lactating, its trabecular bone may be so depleted that it is unable to show bone loss upon ovariectomy, which can affect the results of a bone loss prevention study. Miller 513:25-514:15. Although variability in the retired breeder rat model can occur, it does not necessarily lead to unreliable outcomes, if a baseline control study is performed and the experiment continues a sufficient period of time to allow the transient effects due to lactation to pass. Kinney 1024:21-1025:14.

To be a proper model for osteoporosis, an animal model must, as is the case with the osteoporotic woman, lose bone upon ovariectomy but also have estrogen sensitivity, so that estrogen can be shown to inhibit that bone loss. Miller 512:16-513:4. A drug can

then be compared against the estrogen control to determine its effect. Miller 513:12-22. Although estrogen slowed the decrease in bone density produced by ovariectomy in Dr. Jordan's study, the decrease "was not statistically significant." PTX 218 at 34. However, the Jordan Reference explicitly provided that it is known that estrogen can reverse osteoporosis in rats and that a low dose of estradiol benzoate was purposefully selected to control the weight gain observed upon overiectomy. Id.

V. The Low Dose Patent

The low dose patent is generally directed to the art of dosing regimen design. Hayton 1112:17-21. The concept that the '050 patent adds to the bone loss patents, which claim that raloxifene will prevent or treat postmenopausal osteoporosis, is a particular dosage level at which to administer raloxifene. Specifically, the '050 patent discloses the GGGC study conducted by Lilly, which tested doses of 10, 50, and 200 mg/day and claims a 60 mg/day dose of raloxifene as a method of preventing or treating osteoporosis in postmenopausal women. PTX 17.

Definition of a Person Having Ordinary Skill in the Art for the Low Dose Patent

A person having ordinary skill in the art of the '050 patent would not have to have a specific educational background, but would need experience in the application of dosing regimen design principles to the design or interpretation of clinical trials. Hayton 1113:23-1114:8. Because the '050 patent is directed to using raloxifene at a specific dose

to treat or prevent postmenopausal osteoporosis, a person having ordinary skill in the art would also have to have some knowledge about research regarding postmenopausal osteoporosis and the ADME characteristics of raloxifene to have an understanding of whether the drug could be beneficial in treating or preventing the disease. Miller 574:1-7; Lindstrom 445:5-447:16.

The GGGB Study and the Hong Kong Papers

As discussed above, in September 1992, prior to the filing of the March 2, 1994, application that led to the low dose patent, Dr. Draper designed and conducted the GGGB "proof of concept" study testing doses of 200 and 600 mg/day of raloxifene in order to demonstrate Mr. Black's basic invention in humans. Draper 683:6-20; see PTX 339. Dr. Draper chose the doses to be used in the GGGB study. Draper 683:9-11. According to Dr. Draper, he selected the 200 mg dose because it had previously been deemed a safe dose for humans in Lilly's earlier cancer studies, such as the Buzdar cancer study conducted in 1988. Draper 682:21-24; 711:17-712:3. He chose the 600 mg dose because it was a multiple of the 200 mg dose and was the highest dose that Lilly's toxicologists had informed him would be safe to administer in humans. Draper 680:4-14; 682:21-22; 712:4-10. Dr. Draper testified that, in light of the known bioavailability concerns associated with raloxifene, he wanted to use the highest dose possible of the drug in the proof of concept study in order to ensure that a lack of response did not merely indicate

that a sufficiently high dose had not been administered.[16] Draper 680:15-681:2.

In addition to the 200 mg and 600 mg dosage groups, the GGGB study included a placebo group and an estrogen comparator group in order to observe how the effect seen with raloxifene, if any, compared to that of estrogen. Draper 682:14-20. In January 1993, the results of the GGGB study revealed that both the 200 mg and the 600 mg doses of raloxifene showed statistically significant changes in one or more of the bone markers tested, for the first time unequivocally demonstrating that raloxifene showed activity in humans. Draper at 688:3-689:22.

The 600 mg dose showed a statistically significant change in both serum osteocalcin and serum alkalin phosphate, two biochemical markers of antiresorptive activity in bone. Similar to the 600 mg dose, the 200 mg showed a statistically significant change in serum alkalin phosphate. However, although there was a slight change in the serum osteocalcin with the 200 mg dose, it was not statistically significant. Draper 687:12-689:10; 698:2-10; see PTX 336. According to Dr. Draper, these results established that the 600 mg/day dose would be an effective antiresorptive dose and that the 200 mg/day dose showed "some suggestion" of effectiveness.[17] Draper 689:12-22.

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[16] At a meeting with the FDA on November 7, 1991, Dr. Draper proposed using 50 and 200 mg/day doses in the proof of concept trial. Draper 714:13-21; PTX 562. However, at the time Dr. Draper made this proposal, 200 mg was the maximum dose he thought he would be allowed to administer because he had not yet discussed the allowable upper limits with Lilly's toxicologists. Draper 755:14-756:3.

[17] In 1995, Dr. Jordan published an article entitled "Alternate Antiestrogens and Approaches to the Prevention of Breast Cancer" in which he referenced the results of the GGGB

(continued...)

In March 1993, Dr. Draper presented the results of the GGGB study at the Fourth International Symposium on Osteoporosis in Hong Kong. Shortly after the presentation, various articles were published discussing the results, including an article entitled "Effects of Raloxifene (LY134981 HCl) on Biochemical Markers of Bone and Lipid Metabolism in Healthy Postmenopausal Women," co-authored by Dr. Draper, D.E. Flowers, W.J. Huster, and J.A. Neild ("the Draper Article") (PTX 436), an abstract co-authored by Dr. Flowers and Dr. Huster ("the Draper Abstract") (PTX 324), and reports in the newsletter Scrip World Pharmaceutical News ("the Scrip Article") (PTX 435) and the medical journal The Lancet ("the Lancet Article") (PTX 434), collectively referred to as "the Hong Kong Papers." It is undisputed that Dr. Draper was the Lilly scientist primarily responsible for designing and conducting the GGGB study that is disclosed in the publications and, at trial, Dr. Draper testified that, while the co-authors of the Draper Article and the Draper Abstract assisted with the clinical trial and in drafting the documents, they did not contribute to the selection of the doses.[18] Draper 686:5-687:7.

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[17](...continued)
study, stating that: "Preliminary clinical studies using 200 and 600 mg raloxifene daily in several hundred postmenopausal women demonstrate that the higher daily dose will effectively lower cholesterol and reduce circulating osteocalcin levels." PTX 1936 at 55.

[18] Dr. Draper testified that Dave Flowers was his clinical research associate at the time and was responsible for lining up the study sites, ensuring that the trial material was available, confirming that the education and instructions were correct, and assisting Dr. Draper in putting the data together at the end of the study. Bill Huster was the statistician and Julie Neild was the medical writer who formatted the article for publication. Draper 686:18-687:3.

The Invention and the '050 Patent

After the results of the GGGB study showed activity in humans, but still prior to the application date of the '050 patent, Dr. Draper designed and conducted the GGGC study, which was a dose response trial designed to further characterize the dose response curve[19] of raloxifene. Draper 727:14-728:22. The GGGC study was the first of a number of dose-ranging studies conducted by Lilly in order to determine the minimal effective dose[20] of raloxifene. As mentioned above, Dr. Draper chose 10, 50, and 200 mg/day doses for the GGGC study.

According to Dr. Draper, although raloxifene's complex pharmacokinetic profile (or ADME characteristics) necessitated the proof of concept (GGGB) study to determine whether raloxifene would even be active in humans, it did not drive his dose selection process for the GGGC study because "assays of effectiveness [of any drug] have nothing to do with the pharmacokinetics of the drug." Draper 729:8-25. Dr. Draper testified that he chose the 10 mg dose as a placebo or "no-effect" dose and the 200 mg dose because it had shown promising results in the GGGB study. The 50 mg dose was chosen because it

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[19] Not all drugs have the same dose response curve. The typical dose response curve has an "S" shape when depicted on a graph plotting dose of the drug versus response. At very low doses, most drugs do not provide a significant response. As more and more of a drug is administered, the response grows. At some point, the response reaches an upper plateau at which the response no longer increases, regardless of how much of the drug is administered. Draper 721:12-723:6. At the time Dr. Draper designed the GGGC trial, he did not know what the shape of the dose response curve for raloxifene was because an insufficient number of data points were available. Draper 755:9-13.

[20] The minimal effective dose of a drug is the lowest dose that can be given in which the patient still benefits from the full effect of the drug. Draper 717:1-6.

was "somewhere in between" 10 mg and 200 mg. Draper 699:4-16.

As expected, the results showed no response with the 10 mg dose of raloxifene. The 200 mg dose effected statistically significant changes in both serum alkaline phosphatase and serum osteocalcin, the two bone markers tested in the GGGC study. Draper 700:14-701:5. The 50 mg dose also showed a change in both of those bone markers; however, neither change was statistically significant. Draper 701:6-17. Notwithstanding the absence of statistical significance, Dr. Draper nevertheless believed that there was a possibility that the drug was in fact working at that dose, but that it just needed to develop over a longer period of time in order to be fully effective. Draper 701:18-702:6; 702:20-24; see PTX 17 at col. 13:3-6 ("Because of development over time seen with many bone markers, a raloxifene dose of 50 mg/day will likely be fully active when evaluated during a study of longer duration."). This conclusion was supported by the changes Dr. Draper observed with the 50 mg dose in serum lipids, which are more responsive to change at an earlier time period than the bone markers.[21] Draper 702:7-24; see PTX 17 at col. 13:30-40.

Following the GGGC study, Dr. Draper planned two Phase 3 clinical studies in which different doses of raloxifene would be tested. Based on the effect observed with the 50 mg dose, Dr. Draper chose doses of 30, 60, and 150 mg/day of raloxifene for those studies, reporting on October 28, 1993, to Lilly's Global Plans Approval Committee that

[21] Dr. Draper testified that the bone metabolism effects of drugs such as raloxifene can take as much as a year or two to fully develop. Draper 701:23-702:2.

"[t]he marketed dose is expected to be 60 milligrams." PTX 1687 at EV 7124 434; see also Draper 705:19-706:24. Before the results of the Phase 3 studies were collected, the May 2, 1994, application for the '050 patent was filed, based solely on the results of the GGGC study. The low dose patent disclosed the 60 mg/day dose of raloxifene as a dose that would work to treat or prevent osteoporosis in postmenopausal women. Draper 698:11-699:24; Ettinger 782:2-4; PTX 287. Following a number of longer, more extensive clinical tests conducted after the filing of the low dose patent application, the 60 mg/day dose came to be recognized as the optimal dose of raloxifene for such treatment and prevention. Ettinger 788:6-10.

Advantages of the 60 mg/day Dose

The '050 patent does not identify any advantage to the claimed 60 mg/day dose over any other dose, nor does it identify any "unexpected result" for the 60 mg/day dose. Ettinger 789:11-18; Hayton 1164:17-1165:1. However, approximately four years after the application for the '050 patent was filed, based upon data gathered from a long term clinical trial ("MORE" study),[22] Lilly found that the side effect profile[23] of the 60 mg/day dose evidences two statistically significant advantages over the 120 mg/day. The MORE

[22] The MORE study was a three-year treatment trial with nearly 8,000 women who already suffered from osteoporosis. The trial tested a placebo and 60 mg/day and 120 mg/day doses of raloxifene. Draper 734:5-8.

[23] In terms of efficacy, the two doses were comparable in every measure tested. Draper 736:3-5.

study demonstrated that the 120 mg/day dose is disadvantageous compared to the 60 mg/day dose in terms of overall mortality and incidence of "vasomotor" side effects, *e.g.*, hot flashes. Draper 708:4-23; 709:7-21; PTX 438 at Tbls. 2-3; PTX 661 at EV 307 615 (Tbl. 4).

After the application for the low dose patent was filed, Lilly also found through experience using raloxifene to treat or prevent postmenopausal osteoporosis at a dose of 60 mg/day that such treatment reduces the risk of invasive breast cancer in women so treated. See Ettinger 762:11-18; PTX 1299.

Lilly's Failure to Disclose the Jordan Reference During Prosecution of the '847 Patent

On March 2, 1994, Lilly filed the patent application that originally issued as the '847 patent and later reissued as the '050 patent. Like the bone loss patents, the '847 and '050 patents are directed to a method for using raloxifene to treat osteoporosis and further claims the specific dosage ranges of "about 50 to about 150 mg" ('847 patent), "55 to 65 mg/day" ('050 patent, claim 1), and "60 mg/day" ('050 patent, claim 14). PTX 4; PTX 7; PTX 14; PTX 17. At the same time that Mr. Sales, Lilly's then-patent attorney of record, was in the midst of preparing and submitting the Bryant Declaration to overcome the Jordan Reference cited in the patent prosecution of the bone loss patents, he was also responsible for the prosecution of the '847 patent application. Sales 1926:9-25, 1943:22-1944:5, 1964:20-1965:6, 1970:1-5, 1975:15-1976:11, 1978:6-10. Mr. Sales failed to disclose the Jordan Reference in the prosecution of the '847 patent, and, thus, it was never

considered by the PTO during the prosecution of that patent. Sales 1969:21-25, 1975:15-1976:11, 1978:6-10.

Although Lilly did not disclose the Jordan Reference, the text of the application that led to the '847 patent on its face refers to application Serial No. 920,933, filed July 28, 1992, which is the application for the '763 patent (original bone loss patent). PTX 14 at col. 6:17-21. That application was also cited to the PTO in an Information Disclosure Statement. PTX 4 at 42. After the '763 patent issued on February 28, 1995, Lilly disclosed the existence of the patent to the PTO in an Information Disclosure Statement dated June 22, 1995. Id. at 81.

Lilly's Representations Regarding the Dosage Research During Reissue Proceedings

During reissue proceedings, when the PTO rejected the pending claims of the '050 patent as being obvious, Lilly overcame the rejection by arguing that the claimed dosages were unexpected in view of the bone loss patents, which disclosed raloxifene dosing at 200 mg/day and 600 mg/day. PTX 4 at 75-81 ("While the dosing range of 200 to 600 mg/day does provide sufficient response and is completely pharmaceutically acceptable, Applicant found that a lower dosage range of raloxifene of about 50 mg/day to about 150 mg/day surprisingly results in equivalent benefits as compared to the higher range."). In the '050 reissue application, Lilly also told the PTO that "raloxifene's unpredictability and perceived bioavailability issues" made the dose selection difficult. PTX 7 at 2265-2286 ("Dosage selection for Raloxifene was therefore complicated by the fact that the

drug is extensively metabolized, rapidly cleared from the bloodstream, and heavily serum bound, such that the parent drug is present only at low concentration in the blood."). The Patent Examiner subsequently allowed the '847 patent to issue. PTX 4 at 82.

At trial, Dr. Draper, the inventor of the '050 patent, testified that, because both the 200 and 600 mg/day doses showed promising efficacy in the GGGB trial, at that point, "the highest priority in developing dose response for raloxifene was below 200-milligrams." Draper 726:13-21; see also Draper 715:20-716:2 ("[T]he minimal fully effective dose is usually the target of drug development."). Dr. Draper also testified that raloxifene's metabolism and pharmacokinetic profile did not influence his dose selection for the GGGC study. Draper 729:8-730:6.

Lilly's Failure to Disclose the Schreiber Litigation During Prosecution of the Reissue Patents

In 2002, Barr Laboratories sought FDA approval to market a generic version of raloxifene for prevention of postmenopausal osteoporosis. Barr alleged that Lilly's patents were invalid in view of U.S. Patent No. 5,075,321 ("Schreiber patent"), which purported to describe the use of raloxifene for autoimmune disorders. Although Lilly disagreed with Barr's assertion, on February 27, 2003, Lilly filed three reissue patent applications to clarify that the claims were directed strictly to the treatment of postmenopausal bone loss and did not also encompass the treatment of autoimmune disorders. PTX 5; PTX 6; PTX 7.

The reissue applications included amendments that explicitly recited inhibition of postmenopausal bone loss to treat and prevent postmenopausal osteoporosis. Lilly also informed the PTO of Barr's allegations of invalidity in view of the Schreiber patent, the Jordan Reference, and many of the same references relied upon by Teva in this litigation. PTX 7 at 14-17. After some minor additional amendments to the specifications of the original '117, '763, and '847 patents, the Patent Examiner allowed the reissue application for the '968 patent on February 7, 2006, and the reissue applications for the '049 and '050 patents on March 28, 2006. PTX 5; PTX 6; PTX 7.

On June 2, 2005, Dr. Schreiber filed suit against Lilly alleging, *inter alia*, that: (1) in 1987, Dr. Schreiber confidentially disclosed to Lilly his discovery that raloxifene could be used to prevent and treat autoimmune and immune-mediated diseases such as rheumatoid arthritis and osteoporosis;[24] (2) after proposals for continued collaboration failed, Dr. Schreiber and Lilly terminated their relationship; and (3) in 1994, without Dr. Schreiber's knowledge, Lilly filed patent applications covering Dr. Schreiber's confidential raloxifene disclosures, which issued as the '117, '763 and '847 patents. Docket No. 591 at ¶ 103. Dr. Schreiber's complaint showed that he was aware that Lilly was in reissue proceedings (PTX 409 at ¶¶ 64-68); however, he did not allege inventorship with respect to any of the amended claims of the reissue applications. Id. at ¶¶ 78-83. Although the original '117, '763, and '847 patents were still pending before the

[24] Dr. Schreiber never suggested the use of raloxifene for *postmenopausal* osteoporosis in either the 1987 meeting or throughout the negotiations, however. Lindstrom 379:24-380:4.

PTO, Lilly's in-house patent lawyers failed to submit a copy of Dr. Schreiber's complaint or any other pleadings from that case. Docket No. 591 at ¶ 105. The Schreiber litigation was ultimately dismissed with a consent judgment entered in Lilly's favor on all counts of Dr. Schreiber's allegations, including his allegation that he was the sole or co-inventor of the '763, '117 or '847 patents. According to reports made to us, the consent judgment was entered after a settlement had been reached.

VI. The Particle Size Patents

The particle size patents relate to pharmaceutical formulations for raloxifene. PTX 18. The core concept of Lilly's claimed particle size invention, as described in the '811 patent, is to process the raloxifene particles until the particle size falls "within a specified narrow range." PTX 18 at col. 3:15-17; col. 3:21-23. The '811 patent discloses that, within the claimed particle size range, the raloxifene particles, when formulated, exhibit surprisingly consistent dissolution and bioavailability characteristics.[25] PTX 18 at col. 29:17-21; Byrn 1584:12-14 ("[T]he particle size invention is . . . the discovery that a certain particle-size range, when formulated, gives the same dissolution rate."). Restricting raloxifene's particle size to the limits claimed in the '811 patent also results in manufacturing benefits, which are described in the patent. PTX 18 at col. 3:20-23; col. 29:25-29; col. 29:41-55.

[25] "Dissolution" refers to the rate at which particles dissolve and "bioavailability" refers to the rate at which particles are absorbed into the body.

Lilly has also asserted representative claims of the '719 and '064 patents, which are directed to pharmaceutical compositions comprising 60 mg of raloxifene hydrochloride, a surfactant, and a water-soluble diluent. PTX 20 at col. 39:23-col. 40:8.

Definition of a Person Having Ordinary Skill in the Art for the Particle Size Patents

A person having ordinary skill in the art with respect to the particle size patents would have a Bachelor of Science degree in pharmaceutical sciences, chemistry, chemical engineering, materials engineering, or a related field and should also have either two to five years of experience in the formulation of pharmaceuticals, or advanced training at the Master of Science or Ph.D. level in the field of pharmaceutics. Kibbe 1660:13-1661:4. In light of the interdisciplinary nature of the invention, the person of ordinary skill in the art would be familiar with (or be working with someone who had some experience in) particle size measurement, particulate preparation, and basic statistics. Byrn 1582:3-1583:9.

General Background on the Invention

In early 1993, after receiving positive results from the proof of concept study, Lilly's formulation development group was assigned to formulate raloxifene for Phase 3 testing, and, eventually, commercial use as an oral solid dosage form. Hartauer 1223:22-1224:6. Lilly's expert, Dr. Kerry J. Hartauer, testified that the formulation process for an orally administered drug is generally aimed at three basic goals: (1) developing a dosage

form that is stable, both chemically and physically; (2) developing a dosage form that can be scaled-up in a commercial environment in a cost effective manner; and (3) developing a formulation that delivers the drug to the proper area in the body for exposure to the molecule. Hartauer 1221:3-13.

According to Dr. Hartauer, in the case of raloxifene, one of the greatest initial challenges faced in the formulation process was the molecule's very low aqueous water solubility. Hartauer 1224:10-16. When a drug has low solubility, it has difficulty dissolving in the GI tract, which is the first step in the process of absorption. Hartauer 1225:18-23. In other words, if the drug does not dissolve, it cannot be absorbed into systemic circulation, and gets excreted before there can be any therapeutic effect. Hartauer 1228:18-23. Therefore, Lilly's initial objective in formulating raloxifene hydrochloride was to try to increase the absorption of the molecule. Lilly's first method of doing so was to combine various excipients (additives) that increase solubility with the raloxifene hydrochloride in formulation in order to increase dissolution of the molecule. Hartauer 1230:25-1231:7.

Once Lilly's scientists developed a formulation that demonstrated improved absorption and, ultimately, improved bioavailability,[26] the scientists' focus shifted to studying various physical properties of the raloxifene hydrochloride that could impact

[26] Dr. Hartauer and his co-inventors received U.S. Patent Number 5,811,120 ("'120 patent") for their improved formulation of raloxifene hydrochloride. PTX 1303. Lilly did not assert the '120 patent in this litigation.

solubility and dissolution rate, such as surface area and particle size. Hartauer 1233:10-25. Using multiple milling technologies to change the particle size and surface area, Dr. Hartauer and the co-inventors of the '811 patent, Gordon Arburthnot, Robert Stratford, Wayne Luke, and Brian Dalder, tested various batches of raloxifene with different particle size distributions and surface areas to evaluate how those parameters affected the dissolution rate of the molecule. Hartauer 1239:2-10. Dr. Hartauer first conducted *in vitro* dissolution tests (test tube assays) in which he dissolved four different size lots of raloxifene particles in a 0.1 percent polysorbate 80 aqueous solution and found that the smaller particles with the larger surface area dissolved the most quickly.[27] Hartauer 1247:8-22; see PTX 18 at col. 25:1-30 (Tbls. 6-7). The '811 patent provides that these results can be explained based upon the Noyes-Whitney equation, which relates dissolution to various properties of a solid, such as the effective surface area and particle size. PTX 18 at col. 25:64-66. After collecting the initial data and determining that the changes in particle size, rather than surface area, correlated more closely to the differences in the dissolution performance, Dr. Hartauer and his colleagues shifted their focus solely to particle size. Hartauer 1254:6-18.

In order to determine whether the results seen in the *in vitro* study corresponded to *in vivo* absorption, a rat study was conducted using the same particle size ranges. Lilly's

[27] The different size lots of raloxifene particles were created using various milling techniques, such as ball milling and slurry milling. Hartauer 1250:11-1251:12. Dr. Hartauer testified that, for consistency purposes, the size ranges were chosen based on ranges previously used in Phase 2 efficacy testing. Hartauer 1242:18-23; 1245:7-11.

scientists determined that there was an *in vitro-in vivo* correlation ("IVIVC"), meaning that there was a linear correlation between the percent dissolved *in vitro* and the amount that was actually absorbed in the rats. Hartauer 1257:24-1258:8. Dr. Hartauer testified that an IVIVC is an important research tool which allows the scientists to investigate a parameter, such as particle size, in quick and inexpensive *in vitro* studies, without having to conduct a significant number of more expensive and protracted *in vivo* studies. Hartauer 1255:9-17, 1257:25-1258:12.

Because Lilly's scientists had, up to this point in their research, been testing strictly unformulated raloxifene hydrochloride, they next performed tests to determine whether there was an IVIVC with formulated raloxifene hydrochloride. Using two separate size lots of raloxifene hydrochloride in a formulation (*i.e.*, mixed with excipients) representative of Lilly's commercial tablet formulation, Lilly's scientists tested the dissolution rates in both an *in vitro* study and an *in vivo* study of monkeys and, once again, found that there was an IVIVC. Hartauer 1259:20-1264:4; see PTX 18 at col. 26:50-61 (Tbl. 10); col. 27:5-27 (Tbl. 11).

Feeling confident that they had established that there was a reliable IVIVC when using the 0.1 percent polysorbate 80 solution as the dissolution medium, Lilly's scientists proceeded to test a range of particle size lots of raloxifene that had been formulated into tablets representative of Lilly's commercial product. Specifically, six different lots of raloxifene hydrochloride were mixed with excipients, formulated into tablets, and then

placed in the 0.1 percent polysorbate 80 solution.[28] The dissolution of each tablet was measured at ten, twenty, thirty, and forty-five minutes. Hartauer 1264:17-1266:3. The data collected showed that, despite the fact that each of the lots of raloxifene hydrochloride had a different particle size mean and distribution, they had very similar dissolution profiles, which was contrary to the general understanding that smaller particle sizes dissolve more quickly. Hartauer 1268:20-1269:8. Thus, the invention described in the '811 patent is Lilly's discovery that, when formulated over a particular particle size range, the raloxifene hydrochloride gives a "very consistent dissolution performance." Hartauer 1267:3-14; see LDX 1703. According to Dr. Hartauer, the importance of this particle size "sweet spot" is that Lilly could then be certain that, if it formulated its commercial tablets with raloxifene hydrochloride within the particle size range, individuals taking EVISTA® could be assured that the drug would behave the same way in terms of dissolution and absorption each time it was taken. Hartauer 1267:15-21. Dr. Hartauer also testified that another advantage of the particle size specification is that it allows for better control during the manufacturing process, which results in significant improvements in manufacturing capabilities. Hartauer 1288:5-1289:2.

Lilly's scientists subsequently performed a similar study using an even wider

[28] Dr. Hartauer testified that Lilly used the 0.1% aqueous polysorbate 80 as its official test medium because the formulation scientists had established an IVIVC using it, and, thus, believed it to be predictive of drug absorption in the body. Hartauer 1247:25-1248:5, 1256:4-16, 1258:16-1259:17; PTX 18 at col. 25:10-61, col. 27:45-52; LDX 1702; LDX 1710. Teva has conceded that it is important to conduct dissolution experiments in media that correlate to *in vivo* conditions and that it (Teva) did not conduct raloxifene dissolution experiments in a pure water medium. Docket No. 533, stipulations 5-6.

range of particle sizes and again saw the consistent dissolution. Based on the results of these studies, Lilly adopted the following particle size specification in the '811 patent: a mean particle size between 5 and 20 microns with a d(0.9) value of less than 35 microns. Hartauer 1275:4-11.

Prior Art Addressing the Reduction of Particle Size

A. Noyes-Whitney Equation

The Noyes-Whitney equation shows that the rate of dissolution is expected to increase as effective surface area decreases. PTX 18 at col. 24:45-59. Because effective surface area generally increases as particle size decreases, smaller particles are expected to dissolve faster than larger ones, all other parameters being equal. Byrn 1589:9-1590:13; PTX 1919 at 9. Thus, the Noyes-Whitney equation teaches that reducing the particle size of a slightly soluble compound should increase its dissolution rate, which could potentially increase bioavailability of a drug.

B. The Lantz Article

In 1990, Russell J. Lantz, Jr., published a chapter entitled "Size Reduction" ("the Lantz Article") in Pharmaceutical Dosage Forms: Tablets (Volume Two), edited by Herbert A. Lieberman, Leon Lachman, and Joseph B. Schwartz, which discusses "the process of reducing larger size solid unit masses to smaller size unit masses by mechanical means." PTX 2035 at 107. The Lantz Article recognizes that one advantage

of the size reduction process is an "[i]ncrease in surface area, which may enhance an active ingredient's dissolution rate and hence, its bioavailability. This is particularly important with compounds that are slightly soluble." Id. at 110.

The Lantz Article also discusses various disadvantages associated with the process of reducing particle size, *inter alia*, "a possible change in polymorphic form of the active ingredient, rendering it less (or totally) inactive or unstable" (id. at 112); "possible degradation of the drug as a result of oxidation or adsorption of unwanted moisture due to increased surface area,"[29] (id.); increased particle surface energies which can cause particles to stick together, increasing rather than decreasing particle size, and possibly "decreas[ing] the dissolution rate." Id. The Lantz Article concludes that "[t]he complexity of the [size reduction] process has resulted in few if any theories of general applicability." Id. at 107.

The Limited Nature of Raloxifene Hydrochloride's Consistent Dissolution

Lilly's data establishes that the consistent dissolution profiles that Lilly observed within this particle size range occur only when: (1) the claimed raloxifene is formulated, *i.e.*, mixed with excipients; and (2) the dissolution is carried out in a specific dissolution medium, *i.e.*, the 0.1 percent polysorbate 80 solution. Hartauer 1234:15-1235:5, 1253:19-22, 1267:3-21, 1270:13-15, 1271:7-10, 1272:3-5, 1286:15-20, 1287:7-16; Byrn 1584:12-

[29] Lilly's expert, Dr. Stephen Byrn, testified that oxidation is a particular problem with raloxifene. Byrn 1596:18-25.

16, 1588:2-1589:8, 1635:5-1636:9, 1646:12-15; Kibbe 1692:15-1693:4, 1705:10-16; TDX 1326; PTX 206 at EV 7025 36. Thus, if the raloxifene is unformulated or is dissolved in a different medium, such as plain water, the consistent dissolution does not occur. Hartauer 1270:13-15, 1271:7-10, 1286:15-20; Byrn 1638:12-19; Kibbe 1692:15-1693:4; TDX 1326; PTX 206 at EV 7025 36.

At trial, Lilly's expert, Dr. Stephen Byrn, could not explain Lilly's observation that raloxifene samples having different particle size distributions dissolve at a similar rate. Byrn 1634:14-17. However, Teva presented evidence that both formulating the raloxifene hydrochloride by mixing it with excipients as well as dissolving the raloxifene hydrochloride in the 0.1 percent polysorbate 80 solution rather than plain water speeds up the dissolution rate of the drug. LDX 1703; PTX 18 at col. 28:5-36 (Tbls. 12-13), 13; TDX 1328. The data from Lilly's experiment testing the formulated raloxifene hydrochloride within the claimed particle size range shows that the majority of the dissolution in all the samples took place before the first test point, ten minutes into the dissolution process, in contrast to the dissolution of the unformulated raloxifene, which occurred more slowly. Kibbe 1688:5-1689:22; PTX 18 at col. 25:1-31 (Tbls. 6-7); col. 28:5-36 (Tbls. 12-13). Based on this data, Teva's expert, Dr. Arthur Kibbe, testified that Lilly's consistent dissolution profile only appears consistent because the dissolution times have been sped up and compressed in a way that makes it difficult to readily distinguish between samples without increasing the sensitivity of the test by testing at shorter and earlier time intervals. Kibbe 1688:23-1689:22.

Lilly's Failure to Disclose to the PTO that Consistent Dissolution Was Not Seen in Plain Water

During prosecution, Lilly argued to the examiner that the particle size patent claims were not obvious because they led to the "unexpected result" of consistent dissolution. PTX 8-TA at 431. Lilly argued to the examiner that this result was unexpected because fundamental laws of dissolution suggest that a dissolution time should correlate to particle size; smaller particles should dissolve faster. Id. However, Lilly did not disclose to the examiner that the consistent dissolution was only seen when the raloxifene hydrochloride was dissolved in the 0.1 percent polysorbate 80 solution, but not when it was dissolved in plain water.

Teva's ANDA Amendment and Altered Raloxifene Product

On July 10, 2008, following the Markman hearing and the issuance of the Court's claim construction order, Teva notified Lilly that it had altered its proposed drug product by changing: (1) the particle size manufacturing specification of its bulk raloxifene; and (2) the method of measuring particle size. Teva subsequently provided Lilly with samples of its altered bulk raloxifene (in July through September 2008), as well as samples of tablets containing the altered bulk raloxifene (in December 2008). Following tests conducted by its expert, Dr. Shen Yung Luk, Lilly has conceded that the particle size of Teva's post-July 2008 bulk raloxifene measured before formulation (*i.e.*, before it is blended with excipients and tableted) falls outside of the range claimed in the particle size

patents. The "mean particle size" of Teva's commercial-scale bulk raloxifene is 40.4 microns and its "d(0.9)" value is 81.5 microns, which do not meet the broadest limitations of the particle size claims. Luk 1428:1-1429:18.

However, Lilly contends that Teva's raloxifene product nevertheless infringes Lilly's particle size patents because the raloxifene particles contained within the tablet (*i.e.*, measured after formulation) fall within the claimed size range. According to Lilly, Teva modified its production process in order to produce larger, more fragile raloxifene particles in their bulk form to create the illusion of non-infringement. Lilly claims that, upon processing, those artificially large particles fracture into smaller particles that fall within the size range claimed in Lilly's particle size patents. Teva does not set forth its own particle size measurements of raloxifene extracted from its tablets to contradict Lilly's measurements, but contends that the particle size patents claim only size measurements made on bulk raloxifene *before* it is formulated, not also the particle size of raloxifene *within* a formulated tablet as Lilly claims.

The representative claims of the '811 patent, such as independent claim 1, require that particle size limitations be met by the raloxifene compound when "in particulate form," which is not defined in the '811 patent. PTX 18 at col. 39:25-41. Claim 6 of the '811 patent, which both parties agree is dependent upon claim 1, encompasses pharmaceutical compositions either "formulated using" or "comprising" (*i.e.*, "containing") a raloxifene compound as described in claim 1 (*i.e.*, "in particulate form" and within the particle size limitations). PTX 18 at col. 40:37-41.

While the '811 patent describes the measurement of bulk raloxifene particles *before* being mixed with excipients or carriers, it does not describe the measurement of raloxifene particle size *after* the raloxifene has been mixed with excipients or carriers. Luk 1432:21-1433:9. Nor does it disclose or suggest measuring raloxifene particle size after formulation. Hartauer 1301:25-1302:8. The '811 patent also does not disclose a method of extracting raloxifene from a tablet to measure its particle size and does not provide particle size measurements of the raloxifene in the formulations. Randolph 1819:15-21. Every particle size measurement described in the specification is performed on bulk raloxifene before it is formed into tablets or introduced into capsules. Hartauer 1298:8-22.

Measurement of Raloxifene Particles Extracted From Teva's Tablet[30]

Dr. Luk bases his infringement opinion on a particle size test that he performed on raloxifene particles that he extracted from a single Teva tablet. Luk 1429:19-22. In order to extract the material from Teva's tablet, Dr. Luk developed a protocol consisting of a variety of steps. While Teva's expert, Dr. Theodore Randolph conceded at trial that each

[30] Because, for the reasons detailed below, we find that the disputed claims of the '811 patent are invalid for lack of written description (because we find that the claims must be construed to encompass formulations either containing, or formulated using, raloxifene particles within the claimed size range, but that the scope of those claims overreaches the scope of the inventors' contribution to the field of art as described in the patent specification), we need not address the infringement analysis regarding the particle size limitation further. However, in order to create a complete factual record, we include our factual findings regarding Dr. Luk's methods and his size measurements of raloxifene particles that he extracted from Teva's proposed commercial tablet.

of the steps that Dr. Luk performed as part of his protocol is standard in the industry and not beyond the level of ordinary skill in the art, (Randolph 1829:19-1833:13), it is undisputed that Dr. Luk had never used this protocol before using it to extract the raloxifene particles from Teva's tablet, nor is he aware of anyone else in the industry who has used his exact protocol to extract any API from any formulation. Luk 1437:11-16. Further, because Dr. Luk performed his protocol only once, he could not establish an error rate, *i.e.*, he could not quantify the extent to which flaws or inherent limitations in the protocol could cause deviations in the results. Luk 1457:17-1458:3.

Dr. Luk used the following process to extract and measure the raloxifene particles: He first deaggregated Teva's tablet by breaking it into pieces with his hands by applying gentle pressure with his thumb and forefinger. Luk 1391:14-1392:10. Next, Dr. Luk dissolved a fragment of the tablet into solution and centrifuged the deaggregated tablet, which yielded a yellow[31] mass at the bottom of the tube that was comprised of a mixture of raloxifene and various excipients. Dr. Luk then used density-based separation steps accelerated by centrifugation in order to separate the raloxifene from the other materials in the tablet.[32] Luk 1392:21-1397:21; LDX-1829. After completing the density-based separation steps, Dr. Luk isolated the less dense yellow raloxifene at the top of the tube

[31] Raloxifene is yellow in color.

[32] Teva's expert, Dr. Theodore Randolph, testified that Dr. Luk's extraction protocol required him (Dr. Luk) to collect the centrifuged material containing the raloxifene and place it into a different solvent, which was then centrifuged again to separate the raloxifene from other materials in the tablet. Randolph 1769:9-1770:5.

from the denser white mass of excipients that collected at the bottom of the tube.[33] Luk 1342:2-1343:24; 1392:19-1397:21. Dr. Luk used microscopy, infrared spectroscopy, and visual inspection to determine whether his protocol had resulted in complete separation of the raloxifene in Teva's tablet from the starch and cellulose excipients present in the tablet. Luk 1341:18-1342:1; 1397:22-25; 1400:15-1401:12. In the final step of the protocol, Dr. Luk dried the extracted raloxifene and re-suspended it so that it could be injected into the laser light diffraction apparatus (the method for measuring particle size described in the patents) for measurement. Luk 1343:10-14.

The particle size patents claim a mean particle size "between about 5 and about 20 microns," which the Court construed to mean that the particles have a "mean spherical volume diameter of 4.0 to 24.1 microns." See Docket No. 181. Using laser light diffraction, Dr. Luk found the mean particle size of the raloxifene particles extracted from Teva's tablet to be 17.40 microns. PTX 1999. The particle size patents also refer to at least 90% of raloxifene particles being "less than about 35 microns," which the parties agree means "at least 90% less than about 47.2 microns." Dr. Luk found the 90% size of the raloxifene particles in Teva's tablet to be 38.5 microns. Id.

After obtaining the particle size measurements of the raloxifene contained in Teva's tablet via laser light diffraction, Dr. Luk used both optical and scanning electron

[33] Dr. Randolph testified that Dr. Luk's protocol required him (Dr. Luk) to perform these stages, to wit, mixing the raloxifene-containing material with a solvent, centrifuging the material, and collecting the portion of the separated material that contained the raloxifene, multiple times. Randolph 1769:9-1770:5.

microscopy[34] as methods of corroborating his measurements. Luk 1341:18-1342:1. Although neither optical nor electron microscopy was used to produce an independent measurement of the size of the raloxifene particles, Dr. Luk viewed the images produced by the microscopes to determine whether the sizes of the particles appearing in the micrographs appeared consistent with the values he had reached using laser light diffraction. For example, if large, long raloxifene crystals had appeared on the micrographs, but a relatively small mean value had been reached via laser light diffraction, those results would have been inconsistent. However, Dr. Luk testified that the small raloxifene particles that he observed on the micrographs corresponded with the relatively low mean value of 17.4 microns that he had found using laser light diffraction. Luk 1345:4-1346:15, 1348:19-1349:2. Thus, Dr. Luk determined that the size of the raloxifene particles extracted from Teva's tablet shown in the images produced by microscopy were consistent with the numerical values reached via laser light diffraction.

Teva provided Dr. Luk with one hundred tablets, and, although Dr. Luk testified that he could have measured a second tablet, he performed his measurement protocol only once, using a single Teva tablet. Luk at 1429:19-22; 1431:23-24; 1432:9-15. In reaching his conclusions, Dr. Luk also relied upon his analysis of Teva's bulk API and Teva's intermediate granulation blend, in conjunction with his particle size measurements, all of

[34] Optical microscopy uses light to generate an image, while electron microscopy uses electrons to create an image. Electron microscopy produces a higher level of magnification, effectively providing a "higher zoom level" as compared to the image produced by optical microscopy. Luk 1347:6-25.

which were consistent with his determination that Teva's raloxifene particles break into smaller particles when subjected to the manufacturing and formulation process.

Although Teva did not present evidence to directly contradict the accuracy of Dr. Luk's measurements, its expert, Dr. Theodore Randolph, testified regarding various points in Dr. Luk's protocol where errors could have occurred which would have rendered the results unreliable.[35] For example, at trial, Dr. Randolph testified that Dr. Luk may have used an inadequate sample of raloxifene particles because he failed to verify at each of the "collection points" in his protocol (*e.g.*, when he collected the raloxifene portion from the test tube after centrifugation via pipette and transferred that material to another test tube) that he had collected all of the raloxifene particles (*e.g.*, by weighing the extracted raloxifene and comparing it to the amount by weight of raloxifene contained in the tablet). Randolph 1770:6-1772:20. Dr. Randolph also testified that Dr. Luk's raloxifene sample may not have been completely separated, so his measurements could have been altered by the size of unseparated excipients. Although Dr. Luk performed IR scans to determine that his sample contained only raloxifene, because he did not perform a positive control (*e.g.*, using a separate sample, intentionally place some excipient in with the raloxifene to determine whether the excipient registered on the scan), Dr. Randolph testified that Dr. Luk's analysis may have been affected by

[35] Because Dr. Randolph did not use Dr. Luk's protocol himself to extract and measure raloxifene particles from Teva's commercial tablet to compare with Dr. Luk's measurements, he was only able to testify regarding errors that may have occurred. He could not opine as to whether errors actually occurred during the protocol that affected the reliability of Dr. Luk's measurements.

incomplete separation of the sample. Randolph 1773:24-1774:3.

Evidence Presented Regarding Whether Teva's ANDA Product Is "Non-Solvated"[36]

Claim 7 of the '811 patent requires "a non-solvated crystalline hydrochloride salt of a compound of [raloxifene]" having the claimed particle size range. PTX 18 at col. 40:43-61. Claim 10 of the '811 patent depends from claim 7, and, thus, also requires a "non-solvated" form of raloxifene. PTX 18 at 42:5-9. The particle size patents define a solvate as "an aggregate that comprises one or more molecules of the solute, such as [raloxifene], with a molecule of solvent." PTX 18 at col. 3:61-63. In contrast to solvated forms, non-solvated crystalline raloxifene hydrochloride "is preferred for use in the preparation of pharmaceutical formulations because of the absence of solvent that could affect the patient." PTX 18 at col. 13:28-33.

Lilly's approved product is non-solvated crystalline raloxifene hydrochloride (Hartauer 1276:1-4), which has a molecular weight of 510.05 (PTX 1299 at ¶ 11) and less than 0.5% volatile solvents. PTX 292 at EV111 1097. Teva's raloxifene is crystalline (Randolph 1891:14-22; PTX 519 at T00841), has a molecular weight of 510.05 (PTX 519 at T00034), and has less than 0.36% volatile solvents. PTX 519 at T00833 (total residual solvents and volatiles). However, there was no evidence presented at trial or elsewhere in

[36] Because, for the reasons explicated below, we find that the disputed claims of the '811 patent are invalid for lack of written description, we need not address whether Teva's product is "non-solvated" or includes the excipients required in the '067 and '719 patents. However, in order to create a complete factual record, we include our factual findings regarding these issues.

the documentary evidence regarding how a non-solvated form of a compound is defined. See Byrn 1578:10-1579:15.

The Excipients Required by the '719 and '064 Patents

In addition to the particle size limitation, representative claims 1-3 of the '064 patent are directed to pharmaceutical compositions comprising 60 mg of raloxifene hydrochloride, a surfactant, and a water-soluble diluent. PTX 20 at col. 39:23-col. 40:8. It is undisputed that each tablet of Teva's proposed commercial product contains 60 mg of raloxifene hydrochloride. Luk 1452:11-14; 1466:20-22; PTX 1924 at T00120002. However, the parties dispute whether Teva's tablets contain a water-soluble diluent and a surfactant.

The Court has construed "water-soluble diluent" to mean "a pharmaceutically inert substance, capable of being dissolved in water, that increases the bulk of a tablet." Docket No. 181 at 24. A diluent acts as a filler, which means that it adds bulk to a formulation and is generally used to fill out a tablet. Polli 1551:16-23. Water-soluble diluents are used with relatively insoluble ingredients such as raloxifene, particularly when the amount of active ingredient is small. DTX 1311 at 31. When the diluent is water-soluble, it aids the overall tablet dissolution and helps expose the active ingredients to the dissolution medium. Polli 1552:12-1553:1; Kibbe 1663:10-20. Teva's raloxifene formulation includes Starch 1500, a "pregelatinized" starch that has been processed to generate a water-soluble component, which Lilly contends constitutes a water-soluble

diluent. It is undisputed that Starch 1500 is a diluent and that it is approximately 15% water-soluble (based on the manufacturer's product specification, Starch 1500 may contain from 10% to 20% cold water solubles), or 85% insoluble.[37] Polli 1530:25-1531:8; 1536:21-1537:16; PTX 1926.

The Court has construed "surfactant" to mean "a compound that reduces the surface tension of liquids, or reduces interfacial tension between two liquids or a liquid and a solid." Docket No. 181 at 24. Teva's proposed commercial tablet contains povidone (PVP), which Lilly contends meets this definition. Teva disagrees with the Court's construction and claims that, as the term "surfactant" is commonly used by pharmaceutical formulators, povidone would not be considered a surfactant. Kibbe 1674:14-16. However, it is undisputed that povidone reduces the surface tension of liquids (Polli 1516:24-1517:25, 1518:25-1520:16; PTX 392 at 423), and is surface active

[37] Teva contends that, during the prosecution of the '120 patent, Lilly acknowledged that pregelatinized starch is not water-soluble and that Dr. Hartauer, a co-inventor on the '719 and '064 particle size patents, filed a sworn declaration stating that pregelatinized starch is an "insoluble" diluent. PTX 1305-TA at T 38-47. Initially, we find it improper to import the arguments from the file history of the '120 patent into this litigation. See Abbott Labs. v. Dey, L.P., 287 F.3d 1097, 1104-05 (Fed. Cir. 2002) (relationship between two unrelated patents, although having similar subject matter, one common inventor out of three, and the same assignee, was "insufficient to render particular arguments made during prosecution of [one of the patents] equally applicable to the claims" of the other patent). Moreover, even if we had found the file history of the '120 patent to be relevant to this litigation, the statements made by Lilly and Dr. Hartauer in that prosecution do not contradict the evidence presented at trial. Lilly referred to "starch," not "pregelatinized starch" as the insoluble excipient in the '120 patent prosecution. PTX 1305 at 42-45. While Dr. Hartauer testified in his declaration submitted in support of the '120 patent application that pregelatinized starch "has an insoluble excipient (starch) as its primary diluent," (PTX 1305), he did not deny that it also contains a water-soluble component, which is all that has been alleged by Lilly here.

(Polli 1520:20-1521:16) and amphiphilic, meaning that it has portions that are water-liking and portions that are lipid-liking, which are both characteristics of surfactants. Polli 1518:18-20, 1522:14-1523:15, 1524:9-24; PTX 2031 at 4; PTX 1974 at 45.

Conclusions of Law

I. Standard of Review

As discussed above, Teva has conceded infringement of the bone loss and the low dose patents, but challenges their validity on grounds of obviousness and lack of enablement and their enforceability based on inequitable conduct. With regard to the particle size patents, Teva contends that its generic raloxifene product does not infringe, and that, even if its product did infringe, the particle size patents are invalid on the basis of obviousness and lack of enablement, and are unenforceable due to Lilly's inequitable conduct before the PTO.

On the issue of infringement, Lilly must demonstrate by a preponderance of the evidence that Teva's generic raloxifene product infringes the asserted claims of the particle size patents. Tech. Licensing Corp. v. Videotek, Inc., 545 F.3d 1316, 1327 (Fed. Cir. 2008). To prove infringement, Lilly "must supply sufficient evidence to prove that the accused product or process meets every element or limitation of a claim." Rohm and Haas Co. v. Brotech Corp., 127 F.3d 1089, 1092 (Fed. Cir. 1997).

Because issued patents are statutorily presumed valid under 35 U.S.C. § 282, Teva "has the ultimate burden of persuasion to prove invalidity by clear and convincing

evidence, as well as the initial burden of going forward with evidence to support its invalidity allegation." Titan Tire Corp. v. Case New Holland, Inc., 566 F.3d 1372, 1377 (Fed. Cir. 2009) (citing Tech. Licensing, 545 F.3d at 1327). As the party asserting unenforceability, Teva also has the burden to demonstrate by clear and convincing evidence that Lilly engaged in inequitable conduct. Digital Control, Inc. v. Charles Mach. Works, 437 F.3d 1309, 1313 (Fed. Cir. 2006).[38] Clear and convincing evidence "has been described as evidence which produces in the mind of the trier of fact 'an abiding conviction that the truth of [the] factual contentions are 'highly probable.'" Buildex Inc. v. Kason Indus. Inc., 849 F.2d 1461, 1463 (Fed. Cir. 1988) (quoting Colorado v. New Mexico, 467 U.S. 310, 316 (1984)).

II. The Bone Loss Patents

A. Obviousness

Under the United States Patent Act, a patent cannot be obtained "if the differences between the subject matter sought to be patented and the prior art are such that the subject

[38] In addition to challenging the sufficiency of Teva's evidence on the inequitable conduct issues, Lilly also challenged the legal sufficiency of Teva's asserted defenses in Lilly's Motion for Summary Judgment on Teva's Inequitable Conduct Allegations, filed January 7, 2009. Docket No. 380. The Court reserved judgment on that motion until after the close of evidence. Because, for reasons detailed below, we find that Teva has failed to meet is burden to prove by clear and convincing evidence that Lilly engaged in inequitable conduct in prosecuting its patents, we need not address Lilly's motion for summary judgment on other grounds. Accordingly, we DENY AS MOOT Lilly's Motion for Summary Judgment on Teva's Inequitable Conduct Allegations.

matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103(a). A party seeking to invalidate a patent based on obviousness must demonstrate "by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings and prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1361 (Fed. Cir. 2007) (citations omitted). Obviousness is a question of law based on underlying findings of fact, which include: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art at the time the invention was made; and (4) objective evidence of nonobviousness, if any. Proctor & Gamble Co. v. Teva Pharmaceuticals USA, Inc., 566 F.3d 989, 994 (Fed. Cir. 2009) (citing Graham v. John Deere Co., 383 U.S. 1, 17 (1966)).

Obviousness arises when a skilled individual "merely pursues 'known options' from a 'finite number of identified, predictable solutions.'" In re Kubin, 561 F.3d 1352, 1359 (Fed. Cir. 2009) (quoting KSR Intern. Co. v. Teleflex Inc., 550 U.S. 398, 421 (2007)). Section 103 also bars patentability unless "the improvement is more than the predictable use of prior art elements according to their established functions." 550 U.S. at 417. Obviousness does not require absolute predictability; all that is required is a reasonable expectation of success. Eli Lilly and Co. v. Zenith Goldline Pharmaceuticals, Inc., 471 F.3d 1369, 1377 (Fed. Cir. 2006) (citing In re Longi, 759 F.2d 887, 896 (Fed. Cir. 1985)).

Teva's expert, Dr. Kinney, testified that in his view representative Claim 1[39] of the '086 patent was obvious because: (1) the need to inhibit postmenopausal bone loss was established in the prior art, since it was known at the time that bone loss led to increased incidence of fractures; (2) a single daily dose was disclosed in the '068 patent; (3) the Jordan reference discloses that raloxifene could be administered to inhibit bone loss in ovariectomized rats; and (4) the Turken reference demonstrated the predictive power of the rat model by finding a similar bone-inhibiting effect when tamoxifen was administered to humans. Kinney 976:1-978:1.

However, whether in hindsight the path of the inventor looks obvious is irrelevant. As the Federal Circuit recently recognized in Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc., 520 F.3d 1358 (Fed. Cir. 2008), "In retrospect, [the inventor's] pathway to the invention, of course, seems to follow the logical steps to produce these properties, but at the time of invention, the inventor's insights, willingness to confront and overcome obstacles, and yes, even serendipity, cannot be discounted." Id. at 1364. So it appears here. At the time of the invention, it was known that material chemical differences exist between raloxifene and tamoxifen, which make raloxifene, but not tamoxifen, susceptible to rapid metabolism and glucuronidation. Given this knowledge, the fact that, after testing both antiestrogen compounds, the Jordan Reference suggested that *tamoxifen* could possibly be considered for the prevention of osteoporosis in

[39] The parties' arguments as to Claim 1 apply equally to each of the disputed claims of the '086 patent.

postmenopausal women, but included no specific suggestion that *raloxifene* could have such clinical use,[40] coupled with the extensive evidence adduced at trial regarding bioavailability concerns associated with raloxifene in humans[41] and the fact that Dr.

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[40] According to Teva, the reason neither Dr. Jordan nor any other prior art reference published between the Buzdar report and publication of the results of Lilly's GGGB study suggests the use of raloxifene for the treatment of human postmenopausal osteoporosis is that Lilly had patent protection for raloxifene throughout that time. Teva points to the fact that Lilly received a large number of requests from researchers for raloxifene samples, despite knowledge of raloxifene's rapid metabolism, as evidence that persons of ordinary skill in the art at the time believed that it nevertheless could still be active in the body. However, Dr. Russell explained that, as a purer antiestrogen, raloxifene was a useful research tool because of its low estrogenicity. Russell 664:7-21. Patent protection does not prevent scholarly discourse and publication or even experimentation (as shown by researchers' requests for samples). Moreover, raloxifene was not patented in Europe or Japan at the time, so it was open for development in those markets. Sales 1930:8-15; 2003:8-22. Nevertheless, despite observing similar effects between tamoxifen and raloxifene on bone loss, the Jordan reference makes no mention of the use of raloxifene for use in human postmenopausal osteoporosis and the other references cited by Teva published during the relevant time period cite the Jordan Reference only for its tamoxifen results. See PTX 424; PTX 2173.

[41] Teva contends that a person of ordinary skill in the art would not have had the kind of extensive understanding of ADME-related issues that Lilly's expert, Dr. Lindstrom, possesses. However, there is no prohibition on experts with more than ordinary skill in the art offering opinions from the perspective of one of ordinary skill in the art. Endress + Hauser, Inc. v. Hawk Measurement Sys. Pty. Ltd., 122 F.3d 1040, 1042 (Fed. Cir. 1997) ("To suggest that the [theoretical construct of a person of ordinary skill in the art] applies to particular individuals could mean that a person of *exceptional* skill in the art would be disqualified from testifying as an expert because not ordinary enough.") (emphasis in original). Insofar as Teva is asserting that one of ordinary skill in the art would have no knowledge of ADME characteristics at all, we disagree. The evidence adduced at trial, including the patent specification itself, showed that one of ordinary skill in the art of developing a treatment for human postmenopausal osteoporosis would have understood basic ADME principles and their impact on drug development. The bone loss patents are directed to a method of human drug treatment and the testimony at trial showed that a drug's bioavailability directly affects its ability to be successfully used for treatment purposes. The '086 patent specification identifies the bioavailability problem associated with raloxifene and explains experiments undertaken by Mr. Black to investigate the issue. It is clear that Mr. Black had at least a basic understanding of ADME characteristics, as did other scientists, including Dr. Jordan, who addressed raloxifene's vulnerability to rapid conjugation in publications.

Jordan himself had published at the time regarding the rapid metabolism of compounds with free hydroxyl groups, such as raloxifene, suggesting its unsuitability for this purpose, a person of ordinary skill in the art would not have had a reasonable expectation of success in using raloxifene to treat human postmenopausal osteoporosis.[42] Although at the time of the invention it was known that the glucuronide conjugate of at least one compound, morphine-6, remained active and that certain enzymes could in some cases reverse the effects of conjugation, Teva's expert, Dr. Hayton, conceded that, in the "vast majority" of compounds, glucuronidation deactivates the drug. Hayton 1186:2-5. As discussed above, contrary to Teva's assertions, although the information regarding raloxifene's rapid glucuronidation and the related bioavailability concerns were addressed in internal Lilly documents, those beliefs were not limited to Lilly scientists; they were in fact also widely reported in the literature at the time.

[42] Lilly asserts that the trial evidence supports a second, independent basis for a conclusion of nonobviousness, to wit, that there existed significant uncertainty in the art over the bone effects of raloxifene in light of the Feldman Article's disclosure of results of a rat study in which raloxifene was found not to inhibit bone loss in ovariectomized rats, a conclusion contrary to that reported in the Jordan Reference, but one that was more in line with the thought that a compound that would not have estrogenic effects in sex organs, such as raloxifene, would also not have an estrogenic effect in bone. At trial, both parties' experts battled over whether there were various shortcomings in the Jordan Reference, such as the use of the retired breeder rat model, the measurement technique employed, the statistical analysis applied, and the lack of an estrogen control, that would have led a person of ordinary skill in the art to question its teachings. Based on our review of the evidence and the testimony adduced at trial, we find that, while there were legitimate criticisms that could be leveled against the Jordan Reference, a person of ordinary skill in the art would have relied on the results in the Jordan Reference as reported. However, as detailed above, even though the Jordan Reference was clearly "inching up" on the science, in light of the known bioavailability problems associated with raloxifene at the time, even in light of the other prior art, the Jordan Reference would not have provided a person of ordinary skill in the art with a reasonable expectation of success in using raloxifene to treat postmenopausal osteoporosis in humans.

Further, neither the Turken Article nor the Love Article when considered in conjunction with the Jordan Reference would have rendered the clinical use of raloxifene to treat postmenopausal osteoporosis obvious because those prior art references disclosed only that *tamoxifen* inhibited bone loss in clinical studies, not raloxifene. And, as discussed above, it was known at the time of the invention that tamoxifen's chemical structure differed from raloxifene in that tamoxifen does not have the free hydroxyl groups that make raloxifene susceptible to rapid metabolism and glucuronidation. Finally, the fact that the Jordan Reference, as well as the Jones patent, and the Beall, Moon, and Love Articles[43] were all considered by the PTO during prosecution of the application further supports our conclusion. See Impax Labs., Inc. v. Aventis Pharms., Inc., 468 F.3d 1366, 1378 (Fed. Cir. 2006) ("When the prior art was before the examiner during prosecution of the application, there is a particularly heavy burden in establishing invalidity.") (citations omitted).

For the foregoing reasons, we find that the known concerns regarding the bioavailablity issues associated with raloxifene precludes a finding that a person of ordinary skill in the art would have had a reasonable expectation based on the prior art relied upon by Teva that the drug could be used for postmenopausal osteoporosis in humans. Accordingly, Teva has failed meet its burden to demonstrate by clear and

[43] The Turken Article was not considered by the PTO, but because it discloses the same information as disclosed in the Love Article (i.e., that tamoxifen inhibits bone loss in postmenopausal women), it is merely cumulative.

convincing evidence invalidity of the bone loss patents on the basis of obviousness.

B. Enablement

The statutory basis for the enablement requirement is found in 35 U.S.C. § 112, which provides in relevant part:

> The specification shall contain a written description of the invention and of the manner and process of making and using it, in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same.

Id. ¶ 1. The "enablement requirement is satisfied when one skilled in the art, after reading the specification, could practice the claimed invention without undue experimentation." Sitrick v. Dreamworks, LLC, 516 F.3d 993, 999 (Fed. Cir. 2008) (quoting AK Steel Corp. v. Sollac, 344 F.3d 1234, 1244 (Fed. Cir. 2003)). "[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed." PPG Indus. Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1564 (Fed. Cir. 1996) (quoting Ex Parte Jackson, 217 U.S.P.Q. 804, 807 (1982)). Enablement is determined as of the filing date of the patent application. Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384 (Fed. Cir. 1988).

The Federal Circuit has explained that "the how to use prong of section 112 incorporates as a matter of law the requirement of 35 U.S.C. § 101 that the specification disclose as a matter of fact a practical utility for the invention." In re Cortright, 165 F.3d

1353, 1356 (Fed. Cir. 1999) (quoting In re Ziegler, 992 F.2d 1197, 1200 (Fed. Cir. 1993)). There is a lack of utility under § 101 "when there is a complete absence of data supporting the statements which set forth the desired results of the claimed invention." 165 F.3d at 1356 (quoting Envirotech Corp. v. Al George, Inc., 730 F.2d 753, 762 (Fed. Cir. 1984)).

"In the context of determining whether sufficient 'utility as a drug, medicant, and the like in human therapy' has been alleged, 'it is proper for the examiner to ask for substantiating evidence unless one with ordinary skill in the art would accept the allegations as obviously correct." Rasmusson v. SmithKline Beecham Corp., 413 F.3d 1318, 1323 (Fed. Cir. 2005) (quoting In re Jolles, 628 F.2d 1322, 1325 (Cust. & Pat. App. 1980)). "Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility." In re Brana, 51 F.3d 1560, 1566 (Fed. Cir. 1995) (citing In re Bundy, 642 F.2d 430, 433 (CCPA 1981)).

There is no dispute that, after reading the '086 patent, a person of ordinary skill in the art would be able to administer raloxifene in a single daily dose of 200 mg or 600 mg to humans, as described in Example 5, and that, as is now known, it would have worked to prevent or treat postmenopausal osteoporosis. E.g., Kinney 1086:8-1088:1. However, Teva contends that, assuming the Court finds that the '086 patent is not obvious based on the known bioavailability issues associated with raloxifene, the '086 patent nevertheless

fails to meet the enablement requirement because it discloses no more relevant information regarding human efficacy than that which was disclosed in the Jordan Reference. In other words, if the Jordan rat study could not at the time of the priority filing date predict that raloxifene would work to treat and prevent postmenopausal osteoporosis, then neither would the rat study described in the '086 patent. Thus, Teva's argument implicates the requirement set forth in § 101 (and incorporated into § 112) that the specification disclose as a matter of fact a practical utility for the invention, here, human efficacy.

Initially, we note that Teva's characterization of the '086 patent as including nothing more than that which was disclosed in the Jordan Reference is not entirely accurate. While there is no clinical data included in the '086 patent, the specification addresses the bioavailability issue and provides a rationale derived from the previously undisclosed and unpublished results of the studies Mr. Black conducted in which he administered the glucuronide conjugate found in the bloodstream of the human subjects to rats, to explain why the conjugation would not necessarily be detrimental to the efficacy of raloxifene in humans. PTX 11 at col. 3:28-60. Additionally, the clinical study approved by PTAC is described as Example 5 of the '086 patent, using doses of 200 mg per day and 600 mg per day. PTX 11 at col. 18:15-col. 19:20. Enrollment for the proof of concept study began in May 1992, before the July 28, 1992, priority filing date of the '086 patent. PTX 339 at EV 133 2499.

We assumed for purposes of our preliminary injunction order that, despite the

information included in the '086 patent addressing the bioavailability issue, in light of the significant concerns related to raloxifene's bioavailability and the fact that many Lilly PTAC members were not convinced that raloxifene would be bioavailable in humans despite reviewing Mr. Black's human conjugate studies, a person of ordinary skill in the art would reasonably doubt the utility of the invention. However, upon further review of the facts adduced at trial, relevant Federal Circuit precedent, and the legal standard for demonstrating utility, we find that the disclosure in the '086 patent specification is sufficient even without the later-developed evidence from the GGGB proof of concept study to show utility of the invention for purposes of satisfying the enablement requirement.

While a number of Lilly's PTAC members expressed doubts regarding raloxifene's potential in humans even after reviewing the results of Mr. Black's human conjugate study, a majority of the members of the committee to whom the data was presented did vote in favor of conducting the clinical trial.[44] Furthermore, because there are ethical constraints associated with the commencement of human clinical trials, in order to begin studies such as the proof of concept study described in Example 5 of the '086 patent specification, a trial sponsor must have a basis for believing that the clinical investigation could be successful. According to the Manual of Patent Examining

[44] This majority included Dr. Termine, a bone expert then newly hired to head Lilly's Skeletal Disease program. Mr. Black testified that the data from his human conjugate studies, combined with his explanation for why he did not expect the conjugation of raloxifene to be detrimental to the bioavailability of raloxifene, persuaded Dr. Termine to vote in favor of conducting the clinical trial. Black 203:15-205:3; PTX 708 at EV 7034 748-750.

Procedure, in light of such requirements, the initiation of a clinical trial has a significant impact on the PTO's utility inquiry:

> Before a drug can enter human clinical trials, the sponsor, often the applicant, must provide a convincing rationale to those especially skilled in the art (e.g., the Food and Drug Administration) that the investigation may be successful. Such a rational would provide a basis for the sponsor's expectation that the investigation may be successful. In order to determine a protocol for phase I testing, the first phase of the clinical investigation, some credible rationale of how the drug might be effective or could be effective would be necessary. Thus, as a general rule, if an applicant has initiated human clinical trials for a therapeutic product or process, Office personnel should presume that the applicant has established that the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility.

M.P.E.P. (2008) § 2107.03 at IV. Here, although administration of the raloxifene doses in the GGGB study did not begin until September 1992, enrollment had already begun in May 1992, prior to the priority filing date for the '086 patent. Thus, upon further review of the evidence, we find that the information provided in the '086 patent specification, namely, the results of Mr. Black's human conjugate studies and credible explanation for why conjugation of raloxifene should not be detrimental to the bioavailability of raloxifene, combined with the detailed description of the planned clinical study for which enrollment had already begun at the time of the priority application date, sufficient to demonstrate that the '086 patent application was reasonably predictive of the utility of raloxifene to treat and prevent postmenopausal osteoporosis.

Moreover, as the Court recognized in its preliminary injunction order, even if one of ordinary skill in the art would have reasonably doubted the asserted utility, the law

provides the patentee with the opportunity to present rebuttal evidence sufficient to convince such a person of the invention's asserted utility. See Rasmusson, 413 F.3d at 1323; Brana, 51 F.3d at 1566. Such evidence was introduced here. The results from the GGGB proof of concept study conducted by Dr. Draper demonstrate that raloxifene showed activity in humans at dosages of 200 mg and 600 mg in various bone markers, including serum osteocalcin, which correlates with metabolism in the bone. Draper 687:12-688:2. It is true that enablement or utility is determined as of the application filing date, namely, July 28, 1992. However, even though the results of the GGGB study were not available until early January 1993, slightly more than five months after the priority filing date of the '086 patent, those results are available to overcome the doubts as to the asserted utility since they pertain to the accuracy of a statement set out in the claim specification and go to prove that the disclosure was in fact enabling (*i.e.*, demonstrated utility) when filed. Brana, 51 F.3d at 1567 n.19 (citing In re Marzocchi, 439 F.2d 220, 224 n.4 (Cust. & Pat. App. 1971)).

In conclusion, as previously noted, there is no doubt that a person of ordinary skill, after reading the '086 patent, would be able to administer raloxifene in a single daily dose of 200 mg/day or 600 mg/day to humans as described in Example 5 of the specification and that it would be successful in treating or preventing postmenopausal osteoporosis. The information disclosed in the patent specification regarding Mr. Black's human conjugate studies, coupled with the fact that enrollment in the proof of concept study had begun prior to the priority date of the '086 patent, thereby raising a presumption of utility,

sufficiently distinguishes the '086 patent disclosure from the information disclosed in the Jordan Reference to satisfy the enablement requirement. Additionally, we find the results of the GGGB study showing raloxifene's activity in humans to be sufficient evidence to convince one of skill in the art of the asserted utility, to wit, that raloxifene would work in the treatment and prevention of postmenopausal osteoporosis, if such rebuttal evidence were deemed necessary.[45] For the foregoing reasons, we conclude that Teva has failed to prove by clear and convincing evidence that the bone loss patents are invalid for lack of enablement or utility.

C. Enforceability

Teva contends that the '086 patent is unenforceable because Lilly submitted a declaration to the PTO, dated January 11, 1994, from Dr. Bryant, that intentionally misrepresented the Jordan Reference. "A patent may be rendered unenforceable for inequitable conduct if an applicant, with intent to mislead or deceive the examiner, fails to disclose material information or submits materially false information to the PTO during prosecution." Digital Control, Inc. v. Charles Mach. Works, 437 F.3d 1309, 1313 (Fed. Cir. 2006) (citing Norian Corp. v. Stryker Corp., 363 F.3d 1321, 1330-31 (Fed. Cir. 2004)). The party asserting inequitable conduct has the burden to prove "a threshold of

[45] Although the GGGB study was only the first in a number of tests conducted by Lilly to determine the efficacy of raloxifene in humans, it is sufficient to meet the utility requirement for enablement. See Brana, 51 F.3d at 1568 ("Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development.").

materiality and intent by clear and convincing evidence." Id. (citations omitted). Further, "materiality does not presume intent, which is a separate and essential component of inequitable conduct." GFI, Inc. v. Franklin Corp., 265 F.3d 1268, 1274 (Fed. Cir. 2001) (quoting Manville Sales Corp. v. Paramount Sys., Inc., 917 F.2d 544, 552 (Fed. Cir. 1990)). An intent to deceive "must generally be inferred from the facts and circumstances surrounding the applicant's overall conduct." Paragon Podiatry Lab., Inc. v. KLM Labs., Inc., 984 F.2d 1182, 1190 (Fed. Cir. 1993) (citations omitted). However, "[w]hile intent to deceive the PTO may be found as a matter of inference from circumstantial evidence, circumstantial evidence cannot indicate merely gross negligence." Molins PLC v. Textron, Inc., 48 F.3d 1172, 1181 (Fed. Cir. 1995) (citations omitted).

In his declaration, Dr. Bryant asserted that, at the time of the invention, in his professional judgment, he would have had doubts about the conclusions set forth in the Jordan Reference because: (1) Dr. Jordan's statistical analysis was flawed; (2) the rats used in Dr. Jordan's research were an inappropriate model; (3) Dr. Jordan's measurement techniques were improper, (4) Dr. Jordan was an expert in cancer, not in bone, and his article was not published in a bone journal; and (5) there was conflicting literature (the Feldman Article) regarding raloxifene's inhibitory bone loss effect. PTX 217. On June 9, 1994, after initial review of Dr. Bryant's declaration, the PTO again rejected the bone loss patents. On June 16, 1994, James Sales, the Lilly patent attorney in charge of the prosecution of the bone loss patents at the time, submitted a response to the PTO's final rejection in which he stated that Dr. Bryant's declaration clearly indicates that, when

analyzed, the Jordan Reference would have caused concern to one of ordinary skill in the art as to its actual teaching. PTX 2-TA at 430. The bone loss patents were subsequently allowed by the examiner.

This evidence at best shows that others may have disagreed with Dr. Bryant's assertions to the PTO in which he explained his doubts as of the time of the invention about the findings reported in the Jordan Reference,[46] but it does not establish that the Bryant statements were knowingly false or that his dealings with the PTO evidenced an intent to deceive. Teva's own expert, Dr. Kinney, testified that he believed, not that Dr. Bryant had committed a fraud, only that Dr. Bryant was "mistaken" in his declaration. Kinney 1076:20-23. The principal circumstantial evidence presented at trial regarding Dr. Bryant's dealings with the PTO consists of the following:

In his declaration, Dr. Bryant criticized Dr. Jordan's use of the retired breeder rat model, even though at trial he testified that the best animal model was still up for debate in the field at the time he filed his declaration with the PTO and that he himself had used retired breeder rats in some studies. Bryant 900:22-902:5. In addition, on November 3, 1993, a few months before Dr. Bryant submitted his declaration, he had received an email from Dr. Janet Hock, another Lilly researcher, titled: "To clarify confusion re retired breeder rats." PTX 345 at EV 7093 289. In that email, Dr. Hock wrote that: "Re study

[46] Two of Lilly's bone experts, Dr. Miller and Dr. Russell, both testified, convincingly in our view, that they found nothing in Dr. Bryant's declaration that they regarded to be false or misleading. Russell 639:10-15; Miller 572:15-24. Dr. Miller further testified that, "When I first read it, I thought it was amazingly similar to what I had written, without seeing it, [as] criticisms of the Jordan paper." Miller 572:25-573:4.

using 9 month retired breeders and ralox; *some people* regard this age OXV [sic] as the best model for human E2 [estrogen] deficiency." Id. (emphasis added).[47] However, Dr. Bryant testified that, at the time he wrote his declaration, he had had conversations with other highly regarded scientists in the bone field, including Dr. Kimmel,[48] and, based on those discussions, his conclusion was that the retired breeder rat model was unreliable. Bryant 879:4-882:7. The mere fact that there were certain people in the field who were using or advocating the retired breeder rat model does not establish, either directly or indirectly, that Dr. Bryant intended to deceive the PTO when he expressed his concerns about the model.

Dr. Bryant also criticized Dr. Jordan's use of Student's t-test to complete the statistical analysis published in the study. Admittedly, on a few occasions, a technician in Dr. Bryant's lab at Lilly had applied the Student's t-test inappropriately to analyze data that was never published. Bryant 838:21-842:25. This fact, however, does not support the conclusion that Dr. Bryant's criticism of the method was disingenuous or offered in an effort to deceive the PTO, when he opined that Dr. Jordan's use of Student's t-test to compare multiple groups and report a positive result in a published study was

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[47] We note that it remains unclear whether Dr. Hock was referring specifically to the 9 month-old retired breeder rat or simply to 9 month-old rats in general as the model that some in the field viewed as "the best." Bryant 902:7-903:9; DTX 1303 (Janet Hock Video Deposition) at 117:22-119:23.

[48] In 1996, Dr. Kimmel published an article in which he stated, "However, when doing prevention experiments, the retired breeder female rat is generally unreliable because of both the (likely) already osteopenic condition of the skeleton from which little more bone could be lost, and the period of catch-up growth." PTX 403 at 678-79.

inappropriate.

Nor can we infer an intent to deceive from the fact that, shortly before he submitted his declaration to the PTO, an article that Dr. Bryant co-authored was published which represented that the result reached "is consistent with" the result reported in the Jordan Reference with regard to raloxifene's inhibitory effect on bone loss. One can reach consistent results with another study without necessarily agreeing with the methodology utilized by the other researcher. Dr. Bryant testified that the citation to the Jordan Reference was included in his article because he felt it was important to "be clear about the previous data that is out there." Bryant 818:10-11. It is true that Bryant did not always follow his own guideline in this regard as evidenced by the fact that, even though it was in the literature at the time, he did not also cite to the Feldmann Article in his article. Nonetheless, in other publications and reports dated at approximately the same time he submitted his declaration to the PTO, Dr. Bryant pointed out the Feldmann Article's and the Jordan Reference's conflicting reports regarding the effects of raloxifene in ovariectomized rat models, which is the same point that he made in his declaration. Bryant 875:25-877:21; PTX 225; DTX 1159. In sum, the circumstantial evidence adduced at trial, even when considered as a whole, does not support an inference that Dr. Bryant acted with an intent to deceive in his submissions to or dealings with the PTO.

With regard to Attorney Sales, we find that, at most, the evidence indicates that Mr. Sales was negligent in failing to conduct a more thorough investigation to determine whether the Feldmann Article was the only example of countervailing literature to the

Jordan Reference before submitting his independent statement to the PTO in support of Dr. Bryant's declaration. However, in order to find an intent to deceive, "the alleged conduct must not amount merely to the improper performance of, or omission of, an act one ought to have performed." Molins, 48 F.3d at 1181. Mr. Sales testified that, at the time he filed his response, the Jordan Reference and the Feldmann Article were the only references of which he was aware that addressed raloxifene's effect on inhibiting bone loss and that he therefore believed the statements in Dr. Bryant's declaration to have been true. Because no evidence was presented at trial that would cause the Court to question these representations, we cannot find that, in filing his response, Mr. Sales acted with an intent to deceive the PTO.

Upon review of the totality of the evidence adduced at trial, we find that there is an insufficient basis to satisfy the threshold requirement for establishing the deceptive intent necessary for a finding of inequitable conduct in the prosecution of the '086 patent.[49]

III. The Low Dose Patent

A. Obviousness

1. Prior Art

As discussed above, prior to the filing of the March 2, 1994, application that led to

[49] Because both materiality and intent are required to establish inequitable conduct, we need not address the materiality of the purported false statements attributed to Dr. Bryant and Mr. Sales.

the '050 low dose patent, Dr. Draper designed and conducted the GGGB "proof of concept study" in which he tested doses of 200 and 600 mg/day of raloxifene on humans and the GGGC study in which he tested raloxifene doses of 10, 50, and 200 mg/day. Draper 683:6-20; 698:20-699:16; PTX 339; PTX 287. In March 1993, Dr. Draper presented the results of the proof of concept study at the Fourth International Symposium on Osteoporosis in Hong Kong. For that symposium, Dr. Draper, along with co-authors D.E. Flowers, W.J. Huster, and J.A. Neild, published an article entitled "Effects of Raloxifene (LY134981) on Biochemical Markers of Bone and Lipid Metabolism in Healthy Post-Menopausal Women" ("Draper Article") disclosing the results of the GGGB trial, which had shown that 200 and 600 mg/day doses of raloxifene were effective in preventing postmenopausal osteoporosis in women. PTX 436; Draper 685:23-686:8. Not long after the Draper Article was published, reports regarding the symposium presentation were published in the newsletter Scrip ("Scrip Article") and the medical journal The Lancet ("Lancet Article"). PTX 435; PTX 434. The Draper Article, the Scrip Article, and the Lancet Article are collectively referred to as "the Hong Kong Papers."

The parties dispute whether the Hong Kong Papers constitute prior art to the '050 patent. Section 102(a) provides that:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented *or described in a printed publication* in this or a foreign country, *before the invention thereof by the applicant for patent.*

35 U.S.C. § 102(a) (emphasis added). However, there is an exception to this rule for the inventor's own work that is published within one year of the date of the patent application. In re Katz, 687 F.2d 450, 454-55 (C.C.P.A. 1982). There is no dispute that the Hong Kong Papers constitute printed publications that were published within one year prior to the patent application date. Thus, the disclosure comes within the scope of § 102(a) only if the description contained in the publication is not of the inventor's own work.

Here, the authorship of the Draper Article differs from that of the inventive entity. The '050 patent identifies Dr. Draper and Mr. Black as inventors (see PTX 17), while the Draper Article lists Dr. Draper, D.E. Flowers, W.J. Huster, and J.A. Neild as co-authors, with no indication that the publication describes only Dr. Draper and Mr. Black's work. As Lilly contends, the fact that the Draper Article lists additional co-authors who are not inventors of the '050 patent is not by itself determinative. Katz, 687 F.2d at 455 ("[A]uthorship of an article by itself does not raise a presumption of inventorship with respect to the subject matter disclosed in the article."). However, where, as here, the authorship of a printed publication creates ambiguity regarding inventorship, the burden is on the alleged inventor "to provide a satisfactory showing which would lead to a reasonable conclusion that he is the sole inventor." Id. In other words, Lilly must establish that the relevant portions of the Draper Article (those portions that Teva contends are prior art) describe "the applicant's own work," or the inventive concepts of

Dr. Draper. M.P.E.P. § 2132.01 (Rev. 6, Sept. 2007).

We find that Lilly has successfully made such a showing here. It is undisputed that Mr. Black made the basic invention of using raloxifene to treat postmenopausal osteoporosis. As Lilly asserts, the evidence presented at trial established that Dr. Draper was the Lilly scientist primarily responsible for designing and conducting the GGGB study that is disclosed in the Draper Article and that the listed co-authors assisted with the clinical trial or drafting the article, but did not contribute to the selection of the doses. Draper 686:12-687:7. Dr. Draper testified that he chose to begin with the 200 mg dose because it had been safely used in humans in earlier tests. He also wanted to use the maximum possible dose that would be safe in humans, so he asked Lilly's toxicologists to tell him the highest dose that their research would support, which is how he chose the 600 mg dose. In light of these facts adduced at trial, we find that Lilly has made a sufficient showing that the information disclosed in the cited publications represents the work of Dr. Draper alone. See Katz, 687 F.2d at 455-56 (finding that patentee made a sufficient showing based on inventor's declaration that he was the sole inventor and explanation regarding the co-authors' contribution to the publication). Accordingly, we conclude that the Honk Kong Papers are not prior art to the '050 patent.[50]

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[50] Teva also contends that the selection of the 200 mg/day and 600 mg/day doses cannot be considered Dr. Draper's own work because he was not listed as an inventor on one of the reissued bone loss patents, the '049 patent, which includes a claim to administration of 200 to 600 mg/day of raloxifene. That claim was neither asserted nor litigated in this case.

On June 9, 2009, after the trial was completed and Teva had filed its post-trial briefing, Lilly made a submission to the PTO to add Dr. Draper, with the consent of the listed inventors,

(continued...)

2. Obviousness

Teva does not assert that the bone loss patents are prior art to the low dose patent. Therefore, in light of the known bioavailability problems associated with raloxifene and discussed at length in connection with the bone loss patents, we find that Teva has not satisfied its burden to prove by clear and convincing evidence that the low dose patent would have been obvious for the same reasons that underlie our conclusion that Teva had not succeeded in demonstrating that the bone loss patents would have been obvious. As discussed above, because of the widespread concern regarding raloxifene's rapid glucuronidation and the knowledge that, in the vast majority of drugs, glucuronidation rendered the drug inactive, there was no reasonable expectation that raloxifene could be used to treat or prevent human postmenopausal osteoporosis at all, let alone that it could be effective at a 60 mg/day dose.

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[50](...continued)
Mr. Black and Mr. Cullinan, as a co-inventor on the '049 patent. On June 30, 2009, the PTO granted the Petition to Correct Inventorship and will add Dr. Draper as an inventor of the '049 patent. Lilly has requested that the Court take judicial notice of the filing of the Petition for Certificate of Correction, which is a public document. On June 26, 2009, Teva moved to strike the document [Docket No. 652], arguing that Lilly's reliance on it is both untimely and prejudicial. Because Lilly had ample time to submit such a change to the PTO at any point after Teva initially raised this issue on February 17, 2009, and yet chose not to do so until long after the trial had ended and Teva had filed its post-trial briefing, thereby preventing Teva from cross-examining on this issue or from responding in any other meaningful manner, we find that Lilly's late-breaking submission is plainly prejudicial to Teva. Accordingly, we GRANT Teva's Motion to Strike the Petition for Certificate of Correction.

Nevertheless, we find that the evidence adduced at trial regarding Dr. Draper's contribution to the selection of the 200 mg/day and 600 mg/day doses rebuts any inference raised by the inventorship of the '049 patent and find, for the reasons detailed above, that the Hong Kong Papers are not prior art to the '050 low dose patent.

Teva contends that, because Dr. Draper merely conducted routine testing to reach the 60 mg/day dose, the '050 patent must be ruled invalid as obvious. See In re Geisler, 116 F.3d 1465, 1470 (Fed. Cir. 1997) ("[I]t is not inventive to discover the optimum or workable ranges by routine experimentation.") (quotations omitted); Merck & Co., Inc. v. BioCraft Labs., Inc., 874 F.2d 804, 809 (Fed. Cir. 1989) ("[T]hough requiring time and care, the experimentation needed to arrive at the claimed dosages was nothing more than routine."). It is true that the evidence adduced at trial, including Dr. Draper's own testimony, demonstrates that conducting clinical trials to test for an optimal dose for a drug is generally a routine process and that Dr. Draper's tests "did not incorporate any concepts or ideas that would have been beyond the reach of a person having ordinary skill in the art at that time." Ettinger 782:15-19.

However, it is also well established that "[p]atentability shall not be negatived by the manner in which the invention was made," (35 U.S.C. § 103(a)), unless "the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in light of the prior art." Merck, 874 F.2d at 809 (quotations omitted). Here, in light of what the prior art disclosed about the bioavailabity problems associated with raloxifene, a person of ordinary skill in the art would not have had a reasonable likelihood of success in using a low dose of raloxifene to treat or prevent postmenopausal osteoporosis. This conclusion is the distinguishing fact in the case at bar compared to the cases cited by Teva in support of its contention that the '050 claims would have been obvious through routine testing.

In Geisler, the applicant conceded that the claims were *prima facie* obvious because the claimed range at issue overlapped at its end point with a previously disclosed workable range. Thus, the court found the applicant was unable to rebut the conclusion that, at the time of the invention, a person of ordinary skill in the art would have had a reasonable expectation of success at the time of the invention by demonstrating that the prior art pointed away from the invention. See 116 F.3d at 1470 ("[T]he fact that one group of inventors 15 years earlier may have made an assumption that was contrary to Geisler's test results does not prove that Geisler's results would be regarded as unexpected by one of ordinary skill in the art at the time of Geisler's application."). Contrary to the circumstances in Geisler, the evidence adduced at trial here showed that, *at the time of the invention*, significant concerns regarding raloxifene's bioavailability led to the belief that a large dose of the drug would be necessary to be effective, and thus, that a person of ordinary skill in the art would not have a reasonable expectation of success in using such a low dose of raloxifene.

The facts here are also distinguishable from those presented in Merck. In Merck, the court found the method of use itself to be obvious and thus found that the addition of the dosage claims which produced "only predictable results" did not rebut the obviousness determination because they were not unexpected. 874 F.2d at 809. However, the facts adduced at trial in the case at bar demonstrate that, not only was it nonobvious to use raloxifene to treat or prevent postmenopausal osteoporosis because of the bioavailability issues associated with the drug, but those issues also made its

successful use at a low dose even more unexpected. Thus, after considering the scope and content of the prior art, the level of skill in the art, and the differences between the prior art and the invention of the low dose patent, we hold that Teva has failed to prove by clear and convincing evidence that the '050 patent is invalid as obvious.[51]

B. Enablement

It is clear that the '050 patent discloses treatment of postmenopausal osteoporosis using a raloxifene dose of 60 mg/day, that a person of ordinary skill in the art could prepare and administer such a dose to a postmenopausal woman to treat or prevent postmenopausal osteoporosis, and that it is now known that such a treatment would be effective. See, e.g., Ettinger 804:4-20. However, Teva contends that, because the low dose patent discloses no data specific to the 60 mg/day dose, there was insufficient evidence disclosed in the patent specification to reasonably establish at the time the patent application was filed that the 60 mg/day dose would be operative. Thus, Teva asserts that the '050 patent should be found invalid for lack of enablement based on a failure to show utility of the invention. See Cortright, 165 F.3d at 1356 ("If the written description fails to illuminate a credible utility, the PTO will make both a section 112, ¶ 1 rejection for

[51] Lilly also contends that evidence of unexpected advantages of the 60 mg/day dose of raloxifene supports nonobviousness of the '050 patent. Because we find that the evidence regarding the known bioavailability issues associated with raloxifene precludes a finding that a person of ordinary skill in the art would have had a reasonable expectation that a dose as low as the 60 mg/day dose would be effective, we need not address whether Lilly presented sufficient evidence of unexpected benefits of the 60 mg/day dose to rebut a finding of obviousness.

failure to teach how to use the invention and a section 101 rejection for lack of utility.") (citing M.P.E.P. § 706.03(a), form ¶ 7.05.04). The failure to disclose how to use an invention may support a rejection for lack of utility under section 101 when "there is a complete absence of data supporting the statements which set forth the desired results of the claimed invention." Envirotech Corp., 730 F.2d at 762 (citing In re Ruskin, 354 F.2d 395 (Cust. & Pat. App. 1966)).

As Teva asserts, the '050 patent does not specifically provide data regarding the 60 mg/day dose. However, the '050 patent nevertheless does disclose sufficient information, namely, the results of the GGGC study and associated text regarding the 50 mg/day raloxifene dose, to reasonably establish that the 60 mg/day dose would be operative. The patent provides that doses of raloxifene between 50 and 150 mg/day could be used to inhibit postmenopausal bone loss. PTX 17 at col. 6:4-21. The specification refers to both the GGGB and GGGC studies and discloses the results of the GGGC study which showed that 200 mg/day of raloxifene was fully effective on all bone markers after eight weeks and that the 50 mg/day dose also had an effect on the bone markers, but had not reached statistical significance after eight weeks. PTX 17 at col. 13-14, Tbls. I, II. The specification also provides: "Because of development over time seen with many bone markers, a raloxifene dose of 50 mg/day will likely be fully active when evaluated during a study of longer duration." PTX 17 at col. 13:3-6. At trial, Dr. Draper testified that he based this conclusion in part on the observation in the GGGC study of a statistically significant effect of the 50 mg/day dose in lowering the LDL cholesterol marker, which

responds more quickly to change than the bone markers. Draper 702:7-24. This estrogenic effect of the 50 mg/day dose is also reported in the low dose patent. PTX 17 at col. 13-14, Tbl. II.

Although it is true that this disclosure would not have conclusively established that the 60 mg/day dose of raloxifene was the optimal dose of the drug, such a statement is not required to demonstrate utility of the invention sufficient to satisfy the enabling disclosure requirement. The Federal Circuit recognizes that "[u]sefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development." Brana, 51 F.3d at 1568. Here, the evidence disclosed in the patent specification supporting an effect, although not statistically significant, of the 50 mg/day dose, as well as the explanation and data provided regarding the expectation of its full efficacy in a longer study, coupled with the understanding that the research and development process would continue in order to more fully demonstrate its efficacy, provides sufficient evidence of the invention's utility for purposes of enablement. Thus, we find the disclosure to be sufficient to have precluded any reasonable doubt at the time the '050 patent application was filed regarding the asserted utility of the invention, to wit, that a 60 mg/day dose of raloxifene would work to treat or prevent postmenopausal osteoporosis.

Moreover, even if a person of ordinary skill in the art could have reasonably doubted the utility of the 60 mg/day dose based on the disclosure in the '050 patent specification, the various subsequent studies and clinical trials using the 60 mg/day dose

would undoubtedly be sufficient to confirm that the low dose patent was enabled at the time it was filed. Id. at 1567 n.19 ("[T]hough dated after applicants' filing date, [a declaration supporting usefulness] can be used to substantiate any doubts as to the asserted utility since this pertains to the accuracy of a statement already in the specification. It does not render an insufficient disclosure enabling, but instead goes to prove that the disclosure was in fact enabling when filed (i.e., demonstrated utility)."). Accordingly, for the reasons detailed above, we hold that the '050 patent disclosure is sufficient to demonstrate utility of the 60 mg/day dose, and find that Teva has failed to show by clear and convincing evidence that the '050 patent is invalid for lack of enablement.

C. Enforceability

1. Lilly's Failure to Disclose the Jordan Reference

Teva contends that Lilly committed inequitable conduct in prosecuting the low dose patent when it failed to disclose the Jordan Reference to the PTO. Like the bone loss patents, the low dose patent is directed to a method for using raloxifene to treat and prevent osteoporosis and further claims specific dosage ranges for the drug. Although Attorney Sales was in the process of submitting the Bryant Declaration to overcome the Jordan Reference cited in the '763 (original bone loss) patent prosecution at the same time that he was responsible for the prosecution of the '847 (original low dose) patent application, he did not disclose the Jordan Reference to the PTO during the '847 patent

prosecution. Thus, the Patent Examiner never considered the Jordan Reference during prosecution of the original low dose patent.

This fact notwithstanding, Lilly did tender to the Patent Examiner the co-pending application that eventually issued as the '763 bone loss patent. The text of the co-pending application that led to the '847 patent refers to application Serial No. 920,933, filed July 28, 1992, which is the application for the '763 patent, as well as to the published European counterpart of that application. PTX 14 at col. 6:17-21. The application was also cited to the PTO in an Information Disclosure Statement. PTX 4 at 42. At trial, Attorney Sales testified that, because of the disclosure of the use of raloxifene to treat human osteoporosis in the '763 patent application, he believed it to be the closest prior art to the claims of the '847 patent and, thus, in his opinion, the Jordan Reference was cumulative to that reference in all material respects. Sales 1974:25-1975:5, 1978:6-10.

It is clear that, had the '763 patent application not been disclosed, the Jordan Reference would have been material to the prosecution of the '847 patent since the '847 patent is directed to using a particular dose of raloxifene to treat osteoporosis and the Jordan Reference discloses a rat study using raloxifene to treat bone loss. However, it is well established under Federal Circuit precedent that, "[i]f the withheld information is merely cumulative in light of other references considered by the examiner, the information is not material." Tap Pharm. Prod., Inc. v. Owl Pharm., LLC, 419 F.3d 1346, 1351 (Fed. Cir. 2005) (citing Molins, 48 F.3d at 1179). Had the '763 patent already been issued at the time of the '847 patent prosecution, we agree that it would have been the

closest prior art to the '847 patent. However, in light of the fact that the '763 patent had not yet been issued at the time that the application was cited to the PTO in connection with the '847 patent prosecution, the Patent Examiner likely would have found the information disclosed in the Jordan Reference not to have been cumulative, and thus, material to the prosecution of the '847 patent.

However, even if the Jordan Reference cannot be considered cumulative to the '763 patent application, and thus, material to the prosecution of the '847 patent, "materiality does not presume intent, and nondisclosure, by itself, cannot satisfy the deceptive intent element." Larson Mfg. Co. of South Dakota, Inc. v. Aluminart Prods., Ltd., 559 F.3d 1317, 1340 (Fed. Cir. 2009) (citations omitted). It is not sufficient to demonstrate "the improper performance of, or omission of, an act that one ought to have performed. Rather, clear and convincing evidence must prove that an applicant had the *specific intent* to . . . mislead[] or deceiv[e] the PTO." Star Scientific, Inc. v. R.J. Reynolds Tobacco Co., 537 F.3d 1357, 1366 (Fed. Cir. 2008) (quoting Molins, 48 F.3d at 1181). In conducting this analysis, evidence of subjective good faith militates against a finding of an intent to deceive. Larson Mfg., 559 F.3d at 1341.

Here, Attorney Sales testified that he believed that the '763 patent application was the closest prior art to the '847 patent and that the Jordan Reference was merely a cumulative reference. Although intent most often must be inferred from indirect and circumstantial evidence, "the inference must not only be based on sufficient evidence and be reasonable in light of that evidence, but it must also be the single most reasonable

inference able to be drawn from the evidence to meet the clear and convincing standard." Star Scientific, 537 F.3d at 1366 (citing Scanner Techs. Corp. v. ICOS Vision Sys. Corp., 528 F.3d 1365, 1376 (Fed. Cir. 2008) ("Whenever evidence proffered to show either materiality or intent is susceptible of multiple reasonable inferences, a district court clearly errs in overlooking one inference in favor of another equally reasonable inference."). Given Attorney Sales's testimony, we are unable to find that an inference of intent is the most reasonable inference to be drawn from the evidence. Accordingly, we hold that Teva has failed to prove by clear and convincing evidence that Attorney Sales engaged in inequitable conduct by failing to cite the Jordan Reference during the '847 patent prosecution.

2. Lilly's Representations to the PTO in Conflict with the Inventor's Subjective Beliefs

Teva also claims that the '050 patent is unenforceable because Lilly made misrepresentations to the PTO in connection with the reissue proceedings of the low dose patent. In order to overcome the PTO's initial rejection of the '050 patent claims as being obvious, Lilly argued that: (1) the claimed doses were unexpected in view of the bone loss patents, which disclosed raloxifene dosing at 200 mg/day and 600 mg/day; and (2) raloxifene's "unpredictability and perceived bioavailability issues" made the dose selection difficult. However, Dr. Draper, the inventor of the '050 patent, testified that,

after the results of the GGGB study were received, because the 200 mg/day and the 600 mg/day doses showed promise, at that point, "the highest priority in developing dose response for raloxifene was below 200-milligrams." Draper 726:13-21. He also testified that raloxifene's metabolism and pharmacokinetics profile did not influence his dose selection for the GGGC study, which is where the '050 invention was discovered. Teva contends that the fact that Lilly's representation to the PTO that dose selection would have been difficult for a person of ordinary skill in the art conflicts with Dr. Draper's subjective beliefs and thus shows an intent to defraud.

However, based on Federal Circuit law, an inventor's subjective beliefs are irrelevant to the obviousness analysis. Life Techs., Inc. v. Clontech Labs., Inc., 224 F.3d 1320, 1325 (Fed. Cir. 2000) ("[The obviousness] inquiry, as a matter of law, is independent of the motivations that led the inventors to the claimed invention."). In light of this precedent, we are unable to find that the Patent Examiner would have found information regarding Dr. Draper's thought process material to the reissue proceedings. Further, Teva's effort to prove by clear and convincing evidence that any individual associated with Lilly otherwise mischaracterized the state of the prior art so as to raise an inference of intent to deceive the PTO comes up short.

IV. Enforceability of the '968, '763, and '847 Reissue Patents

Teva contends that the '968, '763, and '847 reissue patents are unenforceable due to Lilly's failure to disclose the Schreiber litigation during reissue proceedings. A patent

applicant's duty to disclose is not limited to disclosing prior art. There is an affirmative duty in any reissue application before the PTO to "call to the attention of the Office any prior or concurrent proceedings in which the patent (for which reissue is requested) is or was involved, such as interferences, reissues, reexaminations, or litigations and the results of such proceedings." 37 C.F.R. 1.178(b). According to the Manual of Patent Examining Procedure, "[l]itigation begun after filing of the reissue application should be promptly brought to the attention of the Office." MPEP 2001.06(c) (2008). "At a minimum, the applicant should call the attention of the Office to the litigation, the existence and the nature of any allegations relating to validity and/or 'fraud,' or 'inequitable conduct' relating to the original patent, and the nature of litigation materials relating to these issues." Id. This duty "runs from the time the reissue application is filed until the reissue application is abandoned or issues as a reissue patent." Id. at 1418(b). The Federal Circuit has found that the fact of litigation is "important because it signals the examiner that other material information relevant to patentability may become available through the litigation proceedings." Nilssen v. Osram Sylvania, Inc., 504 F.3d 1223, 1234 (Fed. Cir. 2007). Accordingly, we find that the existence of the Schreiber litigation was information that would have been material to the reissue proceedings.

A finding of materiality does not end our inquiry, however, because "materiality does not presume intent, and nondisclosure, by itself, cannot satisfy the deceptive intent element." Larson Mfg., 559 F.3d at 1340 (citations omitted). At trial, Teva did not question any Lilly representative who was involved with the prosecution of the reissue

patents regarding the failure to disclose the Schreiber litigation. Teva instead relies solely upon Lilly's failure to present a good faith explanation for the omission to raise an inference of deceptive intent. See Critikon, Inc. v. Becton Dickinson Vascular Access, Inc., 120 F.3d 1253, 1259 (Fed. Cir. 1997) ("Given the materiality and the failure at any point to offer a good faith explanation of the pattern of nondisclosure [of a prior art reference and ongoing litigation], an intent to mislead may be inferred."). As the Federal Circuit recently made clear, to raise an inference of intent to deceive, it is no longer sufficient for an alleged infringer merely to rely upon the patentee's failure to provide a good faith explanation for nondisclosure. Larson Mfg., 559 F.3d at 1340-41 ("[J]ust as merely withholding a reference cannot support an inference of deceptive intent . . . , so too an accused infringer cannot carry its threshold burden simply by pointing to the absence of a credible good faith explanation.") (citations omitted). Because we find that Teva failed to present sufficient evidence to show that any individual substantively involved in procurement of the reissue applications recognized a need to cite the Schreiber litigation or that such a person thereafter intentionally failed to do so for the purpose of deceiving the PTO, we hold that the reissue patents are enforceable.[52]

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[52] Moreover, as recognized above, although intent must often be inferred from indirect and circumstantial evidence, "the inference must not only be based on sufficient evidence and be reasonable in light of the evidence, but it must also be the single most reasonable inference able to be drawn from the evidence to meet the clear and convincing standard." Star Scientific, 537 F.3d at 1366 (citations omitted). Here, the evidence in the record is sufficient to reasonably support non-fraudulent reasons for the non-disclosure of the Schreiber litigation. For example, although the reissue patents had not yet issued at the time that Dr. Schreiber filed his complaint, the Patent Examiner had already allowed the claims in the reissue patents and Lilly had paid the

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For the reasons elucidated in Sections II through IV, *supra*, we hold that the bone loss and low dose patents are valid and enforceable.

V. The Particle Size Patents

A. Claim Construction and Validity of Claims 1 and 6 of the '811 Patent

"[P]atent infringement analysis involves two steps: claim construction and application of the construed claim to the accused process or product." Wilson Sporting Goods Co. v. Hillerich & Bradsby Co., 442 F.3d 1322, 1326 (Fed. Cir. 2006) (citing Markman v. Westview Instruments, Inc., 52 F.3d 967, 976 (Fed. Cir. 1995) (en banc), aff'd, 517 U.S. 370 (1996)). On March 17, 2008, the Court held a Markman hearing during which the parties presented evidence, testimony, and oral argument as to the proper construction of various disputed terms related to the particle size patents and, on June 11, 2008, the Court issued its claim construction order construing the disputed claims. However, since that time, a new dispute regarding claim construction has arisen between the parties. Because determining infringement is a two-step process, the first of which requires the court to ascertain, as a matter of law, the meaning and scope of the relevant claims, we turn first to the claim construction issue.

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[52](...continued)
filing fee. Further, it is undisputed that Dr. Schreiber had not alleged that he was an inventor of the claims restricted to postmenopausal osteoporosis that stood allowed in the reissue patents. In light of these facts, we find that Lilly could have mistakenly believed either that it no longer had a duty to disclose the litigation since the reissue claims had been allowed, but not yet issued, or that the litigation was not material to the reissue proceedings since Dr. Schreiber did not allege that he was an inventor of the reissue claims.

On July 10, 2008, following the Markman hearing and the issuance of the Court's claim construction order, Teva notified Lilly that it had altered its proposed drug product by changing: (1) the particle size manufacturing specification of its bulk raloxifene; and (2) the method of measuring particle size. Teva subsequently provided Lilly with samples of its altered bulk raloxifene (in July through September 2008), as well as samples of tablets containing the altered bulk raloxifene (in December 2008). As discussed above, following tests conducted by its expert, Dr. Shen Yung Luk, Lilly has conceded that the particle size of Teva's post-July 2008 bulk raloxifene measured before formulation (i.e., before it is blended with excipients and tableted) falls outside of the range claimed in the particle size patents. However, Lilly contends that Teva's raloxifene product nevertheless infringes Lilly's particle size patents because the raloxifene particles contained within the tablet (i.e., measured after formulation) fall within the claimed size range.

According to Lilly, Teva modified its production process in order to produce larger, more fragile raloxifene particles in their bulk form to create the illusion of non-infringement. However, Lilly claims that, upon processing, those artificially large particles fracture into smaller particles that fall within the size range claimed in Lilly's particle size patents. Thus, whether the particle size patents claim only size measurements made on bulk raloxifene *before* it is formulated or, by contrast, whether the patents also claim the particle size of raloxifene *within* a formulated tablet, as measured after extraction from the tablet, is of core importance to the infringement analysis.

1. Claim Construction Standard

Claim construction begins with the claim language. Pitney Bowes, Inc. v. Hewlett-Packard Co., 182 F.3d 1298, 1305 (Fed. Cir. 1999) ("The starting point for any claim construction must be the claims themselves."). Absent an express intent otherwise, claim terms should be given "the ordinary and customary meaning . . . that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application." Phillips v. AWH Corp., 415 F.3d 1303, 1313 (Fed. Cir. 2005). This creates an "objective baseline from which to begin claim interpretation." Id. Thus, in interpreting the claims, the court's focus "is not the subjective intent of the parties employing a certain term, but the objective test of what one of ordinary skill in the art at the time of the invention would have understood the term to mean." Centillion Data Sys., LLC v. Convergys Corp., 529 F. Supp. 2d 982, 988 (S.D. Ind. 2008) (McKinney, J.) (citing 415 F.3d at 1313; Innova/Pure Water v. Safari Water Filtration, 381 F.3d 1111, 1116 (Fed Cir. 2004)). However, a claim must also be considered in the context of the intrinsic evidence, including other claims of the patent in question, the specification, and the prosecution history, to ensure that the patentee's use of the disputed terms is consistent with the meaning given by the court. Rexnord Corp. v. Laitram Corp., 274 F.3d 1336, 1342 (Fed. Cir. 2001).

The Federal Circuit has indicated that the specification is "the single best guide to the meaning of a disputed term." Phillips, 415 F.3d at 1315 (quoting Vitrionics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582 (Fed. Cir. 1996)); see also Metabolite Labs., Inc.,

v. Lab Corp. of Am. Holdings, 370 F.3d 1354, 1360 (Fed. Cir. 2004) ("In most cases, the best source for discerning the proper context of claim terms is the patent specification wherein the patent applicant describes the invention."). However, although a claim must be read in light of its specification, particular formulations or preferred embodiments appearing in the specification may not be read to limit the claim. Comark Commc'ns, Inc. v. Harris Corp., 156 F.3d 1182, 1186 (Fed. Cir. 1998) (citations omitted). In sum, as the Federal Circuit explained in Phillips v. AWH Corp.:

> Ultimately, the interpretation to be given a term can only be determined and confirmed with a full understanding of what the inventors actually invented and intended to envelop with the claim. The construction that stays true to the claim language and most naturally aligns with the patent's description of the invention will be, in the end, the correct construction.

415 F.3d at 1316 (quoting Renishaw PLC v. Marposs Societa' per Azioni, 158 F.3d 1243, 1250 (Fed. Cir. 1998)).

Extrinsic evidence, such as dictionaries and treatises, may also be used to assist the court in construing the claim's meaning, but such evidence is afforded less legal significance than that from intrinsic sources. C.R. Bard, Inc. v. U.S. Surgical Corp., 388 F.3d 858, 862 (Fed. Cir. 2004) (citing Vanderlande Indus. Nederland BV v. Int'l Trade Comm'n, 366 F.3d 1311, 1318 (Fed. Cir. 2004)). Additionally, if the meaning of the claim term is unambiguous, and the court can determine that meaning from the intrinsic evidence, it need not rely on extrinsic evidence in construing the claim. Vitronics Corp., 90 F.3d at 1583 (citations omitted).

2. The Proper Construction of the Disputed Terms

As discussed above, the parties dispute whether the claims of the particle size patents are limited to size measurements made on bulk raloxifene *before* it is formulated or whether they also claim a size range for raloxifene particles *within* a formulated tablet. We begin by looking at the language of the claims themselves. Claims 1 and 6 of the '811 patent are representative for this discussion. Claim 1 provides:

> A compound of [raloxifene] and pharmaceutically acceptable salts and solvates thereof, characterized in that the compound is *in particulate form*, said particles having a mean particle size of less than about 25 microns, at least about 90% of said particles have a size of less than about 50 microns.

PTX 18, col. 39:25-41 (emphasis added). Claim 6 states:

> A pharmaceutical composition *comprising or formulated using* a compound according to claim 1, or a pharmaceutically acceptable salt or solvate thereof, in combination with one or more pharmaceutically acceptable carriers, diluents or excipients.

PTX 18, col. 40:36-41 (emphasis added).

The asserted claims all require particle size limitations that must be met by the raloxifene when "in particulate form." PTX 18, col. 39:25-41, 45-46; col. 40:36-61; col. 42:5-9; PTX 20, col. 39:23-32; col. 40:1-7. Teva contends that "in particulate form" should be construed to mean "'bulk' raloxifene powder; i.e., raloxifene before it is mixed with excipients or tableted." Def.'s Tr. Br. at 27. Lilly, on the other hand, argues for a much broader definition of the term. According to Lilly, "in particulate form" as used in the asserted claims should be construed simply to mean "in the form of particles (as compared to dissolved in solution or some other form)." Pl.'s Br. at 26. Lilly contends

that Teva's definition is both contrary to the plain meaning of the term and would read the "or comprising" language out of claim 6.

Lilly argues that Teva's proposed construction of "in particulate form" is contrary to the plain language of the term. Lilly contends that the plain meaning of "in particulate form" does not exclude particles in tablets and presented evidence at trial that, at the time of the invention, the term "particle" was used in the pharmaceutical field to include particles contained in solid dosage forms. E.g., PTX 1987 (1975 article in the Journal of Pharmaceutical Sciences addressing the "effect of compaction on particle size"). Because the patent specification does not explicitly provide a special definition for "in particulate form," Lilly argues that the ordinary meaning of the term cannot be changed. Furthermore, according to Lilly, its construction of "in particulate form" is the only construction that aligns with the language of claim 6 of the '811 patent, which claims both compositions "formulated using" a raloxifene compound as defined in claim 1 as well as compositions "comprising" a raloxifene compound as defined in claim 1.

The parties agree that claim 1 is an independent claim and that claim 6 is dependent upon claim 1. "Under the doctrine of claim differentiation, dependent claims are presumed to be of narrower scope than the independent claims from which they depend." AK Steel Corp. v. Sollac and Ugine, 344 F.3d 1234, 1242 (Fed. Cir. 2003) (citations omitted). Thus, because, as a dependent claim, claim 6 is assumed to be narrower than claim 1, we agree with Lilly that claim 1 must be construed to cover both of the following alternatives explicitly contained in claim 6: (1) pharmaceutical

compositions *formulated using* the compound as described in claim 1; and (2) pharmaceutical compositions *comprising* the compound as described in claim 1. See Schumer v. Lab. Computer Sys., Inc., 308 F.3d 1304, 1311 (Fed. Cir. 2002) ("We have consistently interpreted the word 'or' to mean that the items in the sequence are alternatives to each other.").

It is undisputed that a composition "*formulated using* a compound according to claim 1" is one that is made using raloxifene that falls within the claimed size range as measured before it is mixed with excipients or otherwise formulated. However, the parties dispute what claim 6 means by a pharmaceutical composition "comprising" the compound of claim 1, plus excipients. According to Lilly, "comprising" must be construed to encompass pharmaceutical compositions *containing* raloxifene particles within the claimed size range, as measured within the formulated tablet. Lilly relies upon the Federal Circuit's decision in Exxon Chemical Patents, Inc. v. Lubrizol Corp., 64 F.3d 1553 (Fed. Cir. 1995), to support its position that Teva's raloxifene can infringe at any point during the manufacturing process (*i.e.*, whether entering the process as a raw material or exiting the process as a formulated tablet. See id. at 1558 (holding that claims directed to a "composition . . . comprising" various ingredients covered "a composition that contains the specified ingredients at any time from the moment at which the ingredients are mixed together"). According to Lilly, Teva's construction of "in particulate form" in claim 1 would read the "or comprising" language out of claim 6.

Teva, on the other hand, contends that a person of ordinary skill in the art, reading

the term "in particulate form" in conjunction with the specification, would interpret the term to mean "bulk," or unformulated, raloxifene powder. As Teva asserts, it is well established that the claim language must not be read in isolation, but rather in conjunction with the intrinsic evidence, such as the specification. See Mycogen Plant Sci. v. Monsanto Co., 243 F.3d 1316, 1327 (Fed. Cir. 2001) ("[A] patentee is free to be his own lexicographer, so long as the special definition of a term is made explicit in the patent specification or file history. Thus, we must examine whether these additional sources of intrinsic evidence shed further light on the definition.") (citations omitted); see also Agilent Techs., Inc. v. Affymetrix, Inc., 567 F.3d 1366, 1376 (Fed. Cir. 2009) ("This court generally assigns claim terms their ordinary and customary meanings, according to the customary understanding of a person of ordinary skill in the art who reads them *in the context of the intrinsic record*.") (citations omitted, emphasis added).

It is undisputed that the term "in particulate form" is never explicitly defined in the '811 patent specification. However, the written description repeatedly describes the particle size distribution as a "control parameter" or a "control strategy." E.g., PTX 18 at 26:17-20 ("[T]he decision was made to pursue particle size distribution as a control parameter to ensure consistent performance of the drug product with regards to release of the drug component."); see also PTX 18 at col. 25:58-61 ("This in vitro to in-vivo correlation supports the discriminating ability of the dissolution method, as well as emphasizing the need for a control strategy for either the particle size distribution or surface area of the *bulk* drug substance.") (emphasis added). The evidence adduced at

trial supports the conclusion that a person with ordinary skill in the art would perform quality controls, such as verifying particle size requirements as described in the particle size patents, on the starting materials (*i.e.*, the unformulated raloxifene) rather than the end product (*i.e.*, raloxifene extracted from a tablet). Kibbe 1679:12-1680:16.

Moreover, the specification expressly provides that another function of bringing raloxifene particles within the claimed size limitations is that it results in a significant improvement in manufacturing capabilities. PTX 18 at col. 3:20-23; col. 29:22-55 (providing that the "incoming particle size of the active ingredient" affects later steps in the manufacturing process). Under Federal Circuit law, it is "entirely proper to consider the functions of an invention in seeking to determine the meaning of particular claim language." Medrad, Inc. v. MRI Devices Corp., 401 F.3d 1313, 1319 (Fed. Cir. 2005). It is clear that such manufacturing benefits can be achieved only by controlling the incoming raloxifene particle size (*i.e.*, before the powder enters the manufacturing process), not the particle size after formulation. Byrn 1632:12-1633:2.

Teva contends that its construction is further buttressed by the fact that every particle size measurement described in the specification is performed on bulk raloxifene before it is formed into tablets or granulated with excipients and introduced into capsules. Hartauer 1298:8-12; see PTX 18 at col. 23:57-61; col. 25:32-35; col. 25:59-61; col. 26:24-26, col. 27:29-32, col. 27:61-64, col. 28:47-49. Furthermore, the patent specification distinguishes between the particle size of the raloxifene itself before the granulation and the particle size of the agglomerates of the raloxifene and excipients

formed during the granulation process. PTX 18 at col. 29:41-44 ("It has been discovered that the incoming particle size of the active ingredient also effects [sic] the ultimate particle size distribution of the dry milled agglomerates formed during granulations.").

Teva asserts that these citations to the '811 patent specification demonstrate that Lilly's claim construction not only lacks support in the specification, but is so disconnected from the disclosure provided in the specification that, if adopted, it would render the claims invalid for lack of written description as required by 35 U.S.C. § 112, ¶ 1.[53] According to Teva, because the inventors failed to disclose the notion or importance of measuring the particle size of raloxifene after the granulation or tableting process, they failed to notify the public that their particle size invention was anything other than a "control strategy" for the "bulk drug substance," as the specification explicitly states.[54]

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[53] 35 U.S.C. § 112 provides in relevant part that:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Id. ¶ 1.

[54] In its post-trial reply brief, Lilly moved to strike Teva's argument that Lilly's proposed claim construction would render the particle size patents invalid for lack of written description under 35 U.S.C. § 112, ¶ because Teva did not include such an argument in its Final Contentions. Although Teva never moved to amend its Final Contentions to add an invalidity defense based on lack of written description, we find that the evidence elicited at trial, specifically Dr. Hartauer's testimony during cross-examination, was sufficient to put Lilly on notice that its proposed claim construction could implicate the statutory requirement that a valid patent contain a proper written description and thus has not suffered prejudice. Accordingly, we DENY Lilly's request to strike Teva's contention that, if the particle size patent claims are

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PTX 18 at col. 25:58-61. Thus, to avoid construing the claims in a manner that renders them invalid, Teva contends that we should adopt its proposed construction of "in particulate form." In response to Lilly's contention that Teva's construction of the term reads the "or comprising" language out of claim 6, Teva rejoins that the Federal Circuit's decision in Exxon does not render Teva's interpretation of claim 1 inconsistent with claim 6, but actually confirms that Teva's definition of "in particulate form" in claim 1 can be reconciled with its interpretation of the "comprising" portion of claim 6.

The disputed patent claim in Exxon claimed a lubricating oil "composition . . . comprising" certain ingredients, including a specified amount of "ashless dispersant." Exxon, 64 F.3d at 1556. In Exxon, although the alleged infringer added an ashless dispersant as an ingredient in its composition, as a result of "chemical complexing," the dispersant lost its "ashless" quality once mixed with the other additives in the composition. Id. at 1559. The patentee argued that it had made a sufficient showing of infringement by demonstrating that the alleged infringer "started with the requisite amount of ashless dispersant and . . . ashless dispersant is still present in [the] final product, albeit in ever-changing form." Id. at 1560. The Federal Circuit disagreed, holding that the patentee had not met its burden because, to prove infringement, it had to show "both the presence of ashless dispersant and presence of the required quantity." Id. However, the Exxon court held that the patentee could have met its burden by showing

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[54](...continued)
construed as Lilly requests, they are invalid for lack of written description.

that, even if not present in the final product, the allegedly infringing composition contained the required ingredients at any point during the manufacturing process beginning "at the moment the ingredients are mixed together." Id. at 1558.

Teva contends that, just as the product "comprising" various claimed ingredients in Exxon could be infringed at any point in the manufacturing process from the moment all of the claimed ingredients were mixed together, so too can a composition "comprising" raloxifene in particulate form exist at any point in the manufacturing process, as long as each of the claimed requirements is met. According to Teva's definition, raloxifene remains "in particulate form" only until it is granulated with excipients, at which point the raloxifene becomes embedded with the excipients and forms agglomerates. Therefore, under Teva's definition of "in particulate form," a composition cannot infringe (*i.e.*, contain raloxifene that is both "in particulate form" and within the claimed particle size limits) after the point at which granulation begins. However, it can still infringe at the moment that raloxifene within the claimed size limitations is first mixed with excipients. Thus, Teva contends that claim 6 should be construed to encompass both: (1) pharmaceutical compositions in any form (*e.g.*, granulate, tablet, etc.) that are made from bulk raloxifene which falls within the claimed particle size range (thus meeting the "formulated using" limitation); and (2) pharmaceutical compositions that exist the moment after bulk raloxifene falling within the claimed size range is combined with excipients, but before that combination is subjected to the granulation or tableting steps of the tablet manufacturing process (thus meeting the "comprising" limitation).

We agree with Lilly that Teva's definition of "in particulate form" necessitates a particularly strained and unnatural interpretation of claim 6 that "encompass[es] the fleetingly transitory composition resulting at the instant of admixture but not the mixed product thereafter." Pl.'s Post-Trial Reply at 21. Thus, although the intrinsic evidence supports Teva's construction of "in particulate form," we are unable to legitimately reconcile that construction with the language of claim 6, and therefore, must conclude that such a construction would read "or comprising" out of that claim. However, we also agree with Teva that Lilly's construction extends the definition of "in particulate form" beyond the notice that the '811 patent specification provided to the public, thereby rendering the claims invalid for lack of written description.

The Federal Circuit has explained that "the purpose of the written description requirement is to 'ensure that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor's contribution to the field of art as described in the patent specification.'"[55] ICU Medical, Inc. v. Alaris Medical Sys., Inc., 558 F.3d 1368, 1376 (Fed. Cir. 2009) (quoting Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916, 920 (Fed. Cir. 2004)). "It has long been the case that a patentee can lawfully claim only what he has invented and described, and if he claims more his patent is void."

[55] In Ariad Pharmaceuticals, Inc. v. Eli Lilly and Co., 2009 WL 2573004 (Fed. Cir. Aug. 21, 2009), the Federal Circuit recently agreed to hold a rehearing *en banc* to address whether the patent code mandates a written description of the invention separate from the enabling language, and, if so, what the scope and purpose of that requirement is. However, under current Federal Circuit law, a separate written description requirement exists, and thus, we analyze this case in line with that precedent.

Carnegie Mellon Univ. v. Hoffmann-LaRoche Inc., 541 F.3d 1115, 1122 (Fed. Cir. 2008) (quotations omitted). Whether the written description requirement is satisfied is a fact-based inquiry that depends on the nature of the invention and the knowledge of one skilled in the art at the time the invention is made and the application is filed. Id.

Here, the '811 patent specification clearly limits Lilly's invention to a particle size range on unformulated raloxifene, and does not demonstrate that the inventors intended to encompass a particle size range on raloxifene after granulation and tableting. Although Dr. Hartauer testified that the inventors considered measuring the particle size of raloxifene extracted from a tablet (Hartauer 1298:23-1299:1), they neither disclosed this idea in the '811 patent, nor performed any tests to determine how the granulation or tableting process could affect particle size to determine whether bulk lots of raloxifene that fell outside of the particle size ranges before formulation would be altered during the granulation or tableting process in such a way that would bring them within the claimed ranges after formulation.[56] Hartauer 1290:11-13, 1293:1-5, 1293:14-20, 1294:11-15,

[56] For example, in one instance, the patent specification discloses dissolution tests performed on two batches of granulated raloxifene material; one batch (Lot 5B) was formulated using bulk raloxifene that had been pin-milled down to a 9-micron mean particle size, which meets the claimed particle size limitation, and the other batch (Lot 5A) was formulated using bulk raloxifene that had been slurry-milled to a 48.1-micron mean particle size, which falls outside of the claimed particle size limitation. PTX 18 at col. 26:20-27:52; Tbl. 9. For each of these two batches, the patent discloses the particle size distribution only for the bulk raloxifene that was used to make the granulation, but does not disclose particle size information for raloxifene extracted from either of the two granulated batches. Hartauer 1293:1-5, 14-20.

At trial, Lilly's expert, Dr. Luk, testified that one reading the '811 patent in 1996, without actually measuring the raloxifene in formulated product, would not know whether raloxifene subjected to granulation and/or tablet compression steps would increase in particle size,

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1296:25-1297:3, 1299:2-17.

Moreover, it is clear from the evidence adduced at trial that extracting particles of an API from a formulated tablet for purposes of particle size measurement was not at all a routine practice in 1996 so as to make it unnecessary for the inventors to specify the procedure for doing so. Thus, after reading the patent, a person of ordinary skill in the art would not understand how to extract raloxifene particles from formulation in order to determine whether they fall within the claimed particle size range and, in fact, would have no indication that size measurements on anything other than unformulated raloxifene would bear any relevance to the invention. Accordingly, based on the disclosure in the '811 patent, a person of skill in the art would not understand the inventors of the particle size patents to have invented anything other than "a control strategy for . . . the particle size distribution . . . *of the bulk drug substance*," as expressly provided in the specification. PTX 18 at col. 25:60-61 (emphasis added).

For the reasons detailed above, we find that the only claim construction that is consistent with the language of the claims, renders them invalid for lack of written description. Under Federal Circuit law, claims are generally construed so as to sustain their validity, if possible. Whittaker Corp. by Technibilt Div. v. UNR Indus., Inc., 911 F.2d 709, 712 (Fed. Cir. 1990) (citations omitted). However, the Federal Circuit also

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[56](...continued)
decrease, or stay the same. Luk 1434:1-8. Thus, without measuring the raloxifene particle size extracted from the granulation, one applying Lilly's claim construction would not know whether the raloxifene in those lots fell within the claimed range.

"admonishe[s] against judicial rewriting of claims to preserve validity." Rhine v. Casio, Inc., 183 F.3d 1342, 1345 (Fed. Cir. 1999) (citations omitted). Therefore, when the only proper claim construction would render the claims invalid, as is the case here, "the axiom does not apply and the claim is simply invalid." Id. Accordingly, we must find that claims 1, 3, 6, 7, and 10 of the '811 patent and claims 1, 2, and 3 of the '064 patent are invalid for lack of written description.[57]

B. Enforceability

Teva also contends that Lilly engaged in inequitable conduct in prosecuting the particle size patents when it failed to disclose to the PTO that the consistent dissolution profiles were seen only when the formulated raloxifene was dissolved in the 0.1 percent polysorbate 80 solution and not in plain water. According to Teva, this information was highly material because it convinced the Patent Examiner both that the invention led to unexpected results and also to allow broader claims than otherwise might have been allowed. Teva contends that the fact that Dr. Hartauer explicitly relied upon the dissolution tests conducted in water in Lilly's '120 patent (which discloses formulations that increase bioavailability (PTX 1303 at col. 1:65-col. 2:4)) is sufficient evidence that

[57] All of the asserted claims require particle size limitations that must be met by raloxifene "when in particulate form." Because, for the reasons detailed above, we find the claims including the "in particulate form" limitation to be invalid for lack of written description, we need not address the infringement analysis or Teva's validity challenges based on obviousness and lack of enablement.

Dr. Hartauer intended to deceive the PTO by failing to disclose the information during prosecution of the particle size patents.

However, Lilly's particle size invention described consistency seen using the medium in which Lilly had established an IVIVC. The evidence adduced at trial demonstrated that Lilly found the IVIVC when raloxifene particles were dissolved in the 0.1 percent polysorbate 80 solution, not in plain water. Byrn 1581:13-22. Lilly's expert, Dr. Byrn, testified that, once an IVIVC was established, results of dissolution testing in other, non-predictive media were irrelevant to the claimed subject matter and its intended use. Byrn 1604:11-1605:2. Dr. Hartauer testified that, prior to the filing of the original 1996 application, he had concluded for multiple reasons that raloxifene dissolution results in pure water had no practical significance. Hartauer 1272:7-22; PTX 206 at EV 7025 36. Moreover, Teva has stipulated for purposes of this litigation that it is important to evaluate dissolution in media predictive of *in vivo* performance and that Teva itself does not evaluate dissolution of raloxifene in pure water. Docket No. 533, stip. 5.

Given these facts, we are unable to conclude that Teva has met its burden to prove by clear and convincing evidence either that the undisclosed information in connection with the medium used for the dissolution tests was material or that Lilly intended to deceive the PTO by failing to disclose that information. Thus, we find that Teva has failed to show that Lilly engaged in inequitable conduct when it failed to disclose to the PTO that the consistent dissolution profiles were only observed when the formulated raloxifene was dissolved in the 0.1 percent polysorbate 80 solution.

VI. Conclusion

For all of the reasons explicated above, the Court hereby declares that:

(1) Teva has failed to prove by clear and convincing evidence that any of claims 1-3 of the '086 patent; claims 1, 3, and 4 of the '968 patent; claims 1, 2, 5-9, 11, 12, 19, 20, 28, 31, 33, and 34 of the '049 patent (collectively "the bone loss patents"); and claims 1, 2, 5, 7, and 12-15 of the '050 patent (or "low dose patent") are invalid as obvious under 35 U.S.C. § 103; are invalid for lack of enablement under 35 U.S.C. § 112 or § 101; or are unenforceable due to inequitable conduct. The asserted claims of the bone loss and low dose patents are, therefore, neither invalid or unenforceable.

Teva stipulated that if the asserted claims of the bone loss patents and the low dose patent are neither invalid or unenforceable, then its actions regarding its raloxifene product that is the subject of ANDA No. 78-193 constitute infringement of the asserted claims of the bone loss patents and the low dose patent. The Court therefore finds that Teva has infringed and threatens in the future to infringe claims 1-3 of the '086 patent; claims 1, 3, and 4 of the '968 patent; claims 1, 2, 5-9, 11, 12, 19, 20, 28, 31, 33, and 34 of the '049 patent; and claims 1, 2, 5, 7, and 12-15 of the '050 patent.

(2) Teva has proven by clear and convincing evidence that claims 1, 3, 6, 7, and 10 of the '811 patent and claims 1-3 of the '064 patent are invalid for lack of written description. Lilly stipulated that if claims 1, 3, 6, 7, and 10 of the '811 patent and claims 1-3 of the '064 patent are invalid, it will not assert against Teva any other claims of the '811, '064, and '719 patents. The Court therefore finds that the asserted particle size

patent claims are invalid for lack of written description under 35 U.S.C. § 112.

Accordingly, it is hereby ordered that:

(1) Pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval of the raloxifene product that is the subject of ANDA No. 78-193 SHALL NOT BE a date earlier than the latest date of expiration of Lilly's bone loss and low dose patents; and

(2) Pursuant to 35 U.S.C. § 283 and 35 U.S.C. § 271(e)(4)(B), Teva and its officers, agents, servants, employees, privies, and others acting for, on behalf of, or in concert with it are PERMANENTLY ENJOINED from the commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of the raloxifene product that is the subject of ANDA No. 78-193 or any raloxifene product not colorably different therefrom prior to the latest date of expiration of Lilly's bone loss and low dose patents. This permanent injunction order is effective immediately upon the entry of this ruling on this Court's docket. Final judgment shall be entered accordingly.

IT IS SO ORDERED.

Date: 09/23/2009

SARAH EVANS BARKER, JUDGE
United States District Court
Southern District of Indiana

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